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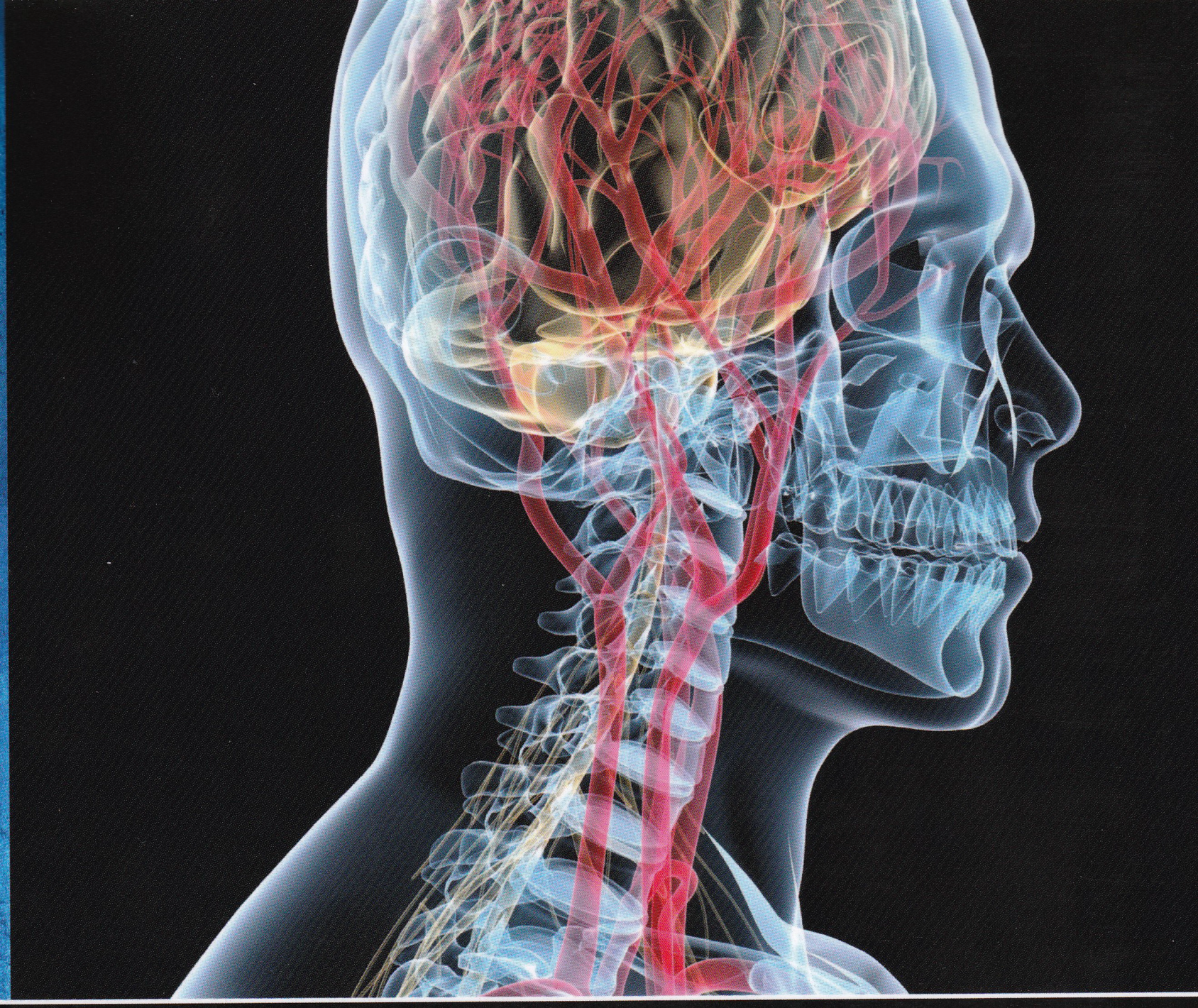

Physiology

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Physiology

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Unit 1

Body Fluids

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1 Basic Concepts

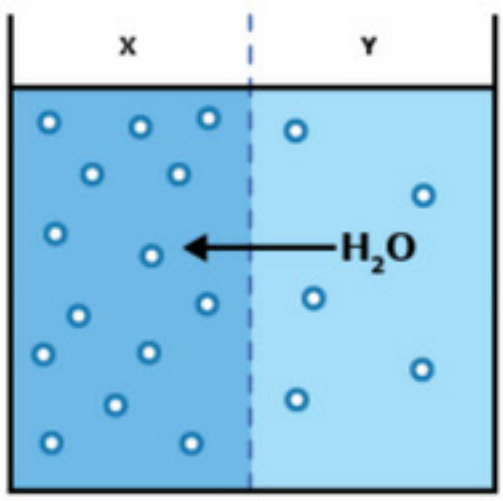
1.1 Introduction

▲ **Figure 1–1.1** Distribution of Body Fluids

- Total body water is about 60% of body weight (70 kg body weight = 42 L)
- ICF = 2/3 of total body water (28 L)
- ECF = 1/3 of total body water (14)
- ECF = ISF (3/4) + Plasma water (1/4)
- ECF = ISF (2/3) + Blood volume (1/3 = 5 L)

1.2 Extracellular Fluid (ECF) vs. Intracellular Fluid (ICF)

Only osmotic forces determine the distribution of fluid between the intracellular and extracellular compartments. Osmosis is simply the net diffusion of water across a membrane. Consider the following model:



▲ **Figure 1–1.2** Principle of Osmosis

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- Two compartments separated by a semipermeable membrane, permeable to water but not to the dissolved substance.
- The concentration of the dissolved substance determines the concentration of water (↑ concentration of dissolved substance ↓ concentration of water).
- The water diffuses from the higher concentration in *Y* to the lower concentration in *X*.
- If the membrane was permeable to the dissolved substance, it would equalize its concentration between the two compartments, and there would be no water concentration gradient and no net diffusion of water (osmosis).
- To have an osmotic effect across a membrane, it *cannot* penetrate the membrane. The concentration of all dissolved substances in a compartment that cannot penetrate the surrounding membrane is the *effective osmolarity*.
- In the extracellular fluid, the main dissolved substance that cannot penetrate the cell membrane is sodium (Na^+). A negative ion must remain with the ECF Na^+ to maintain electrical neutrality; for example, Cl^-, HCO_3^-, and HPO_4^-.
- Thus, ECF effective osmolarity is approximately 2x [Na^+].
- Glucose penetrates membranes slowly and contributes some osmotic effect, particularly with hyperglycemia. Urea easily penetrates most membranes, but not all (blood-brain barrier, sections of nephron). Some include urea in the ECF effective osmolarity; others ignore it.

The following is the standard formula:

$$\text{Effective osmolarity (ECF)} = 2\,(Na^+)\ \text{mEq/L} + \frac{\text{glucose mg\%}}{18} + \frac{\text{urea mg\%}}{2.8}$$

Glucose in mg% divided by 18 gives mM, the concentration of individual particles.

It is the concentration of individual particles that creates the osmotic effect (mOsm/L).

mM/L = Concentration of molecules per liter.
Isotonic fluid is about 280–285 mOsm/L.
Step I tends to round this off to 300 mOsm/L.
Isotonic: NaCl = 300 mOsm/L = 150 mM/L
Glucose = 300 mOsm/L = 300 mM/L

- **Hypernatremia**—Water diffuses out of cells and they "shrink."
- **Hyponatremia**—Water diffuses into cells and they "swell."

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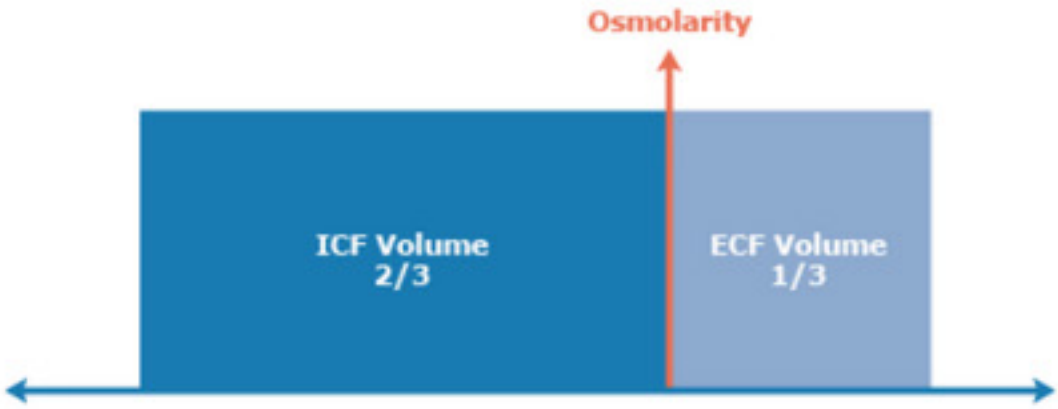
2 Darrow–Yannet Diagram

The Darrow-Yannet diagram is a standard model to display changes in body osmolarity and ECF versus ICF volume.



▲ **Figure 1–2.0** Darrow-Yannet Diagram

Volumes are on the *X*-axis and body osmolarity on the *Y*-axis. In a steady state, the intracellular and extracellular osmolarities are the same. Water always equilibrates across the cell membrane.

Questions involving this figure are generally qualitative, deciding ↑, ↓, or no change.

A specific sequence should be followed:

1. **ECF volume:** a gain in fluid ↑, a loss in fluid ↓ regardless of the composition of the fluid.
2. **Osmolarity:** depends on concentration of Na^+ in the ECF (but remember hyperglycemia or infusion of hypertonic mannitol).
3. **ICF volume:** this depends on the conclusion in 2; osmolarity ↑, cells shrink, osmolarity ↓, cells swell.

2.1 Classification (All Gains and Losses Are Through the ECF)

- **Loss of hypotonic fluid:** sweating, hypotonic urine (diabetes insipidus, alcohol).
- **Loss of isotonic fluid:** diarrhea (except infant), vomiting, hemorrhage.
- **Loss of hypertonic fluid:** SIADH, inappropriate ↑ urine osmolarity.
- **Gain of hypotonic fluid:** tap water (same as distilled water), hypotonic saline.
- **Gain of isotonic fluid:** isotonic saline.
- **Gain of hypertonic fluid:** hypertonic saline, hypertonic mannitol.
- **Gain of NaCl:** ingesting salt tablets.
- **Loss of NaCl:** loss of 1 L sweat, drink 1 L of tap water.

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2.2 Three Complex Situations

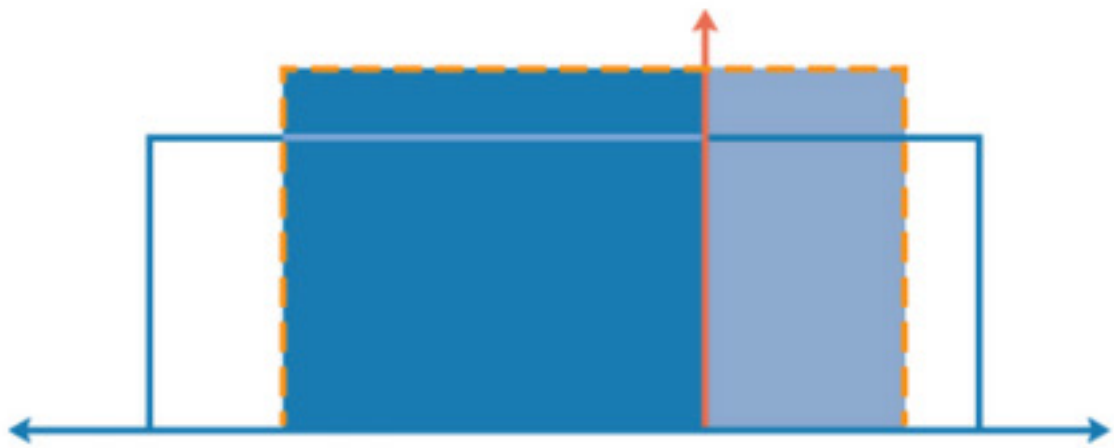
1. **Primary adrenal insufficiency:** loss of aldosterone results in sodium + water loss (assume isotonic loss). Partial volume replacement with tap water causes hyponatremia. Therefore, the net effect is ↓ ECF volume, ↓ body osmolarity.

   Note: Salt wasting occurs with the loss of any body fluid. Partial volume replacement with tap water results in; ↓ ECF volume ↓ osmolarity (hyponatremia).

2. **Dehydration receiving isotonic saline:** osmolarity ↓.
3. **Hyponatremic volume depletion receiving isotonic saline:** osmolarity ↑.

2.3 Graphical Depictions (Solid Lines = Original State)

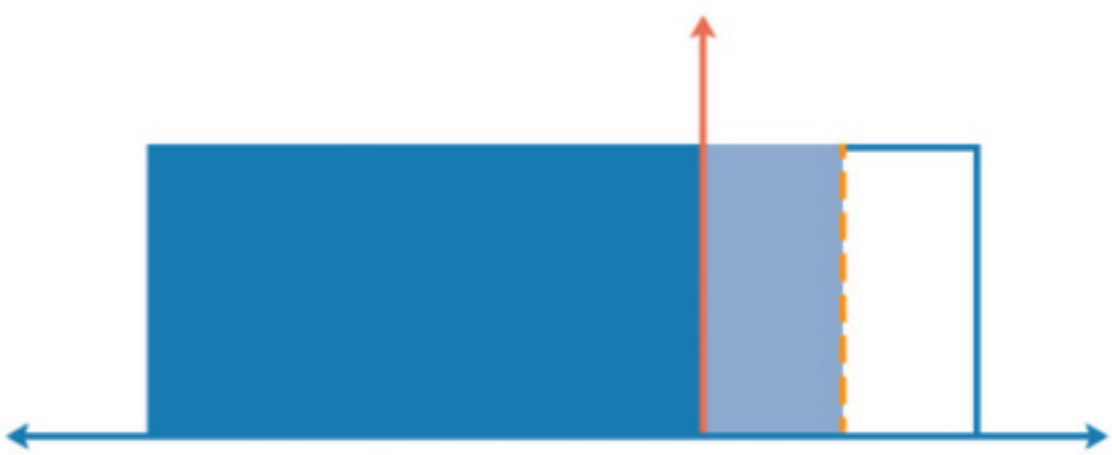
1. **Loss of Hypotonic Fluid**



ECF volume ↓ Osmolarity ↑ ICF volume ↓

▲ **Figure 1–2.3A** Loss of Hypotonic Fluid

2. **Loss of Isotonic Fluid**



ECF volume ↓ Osmolarity n/c ICF volume n/c

▲ **Figure 1–2.3B** Loss of Isotonic Fluid

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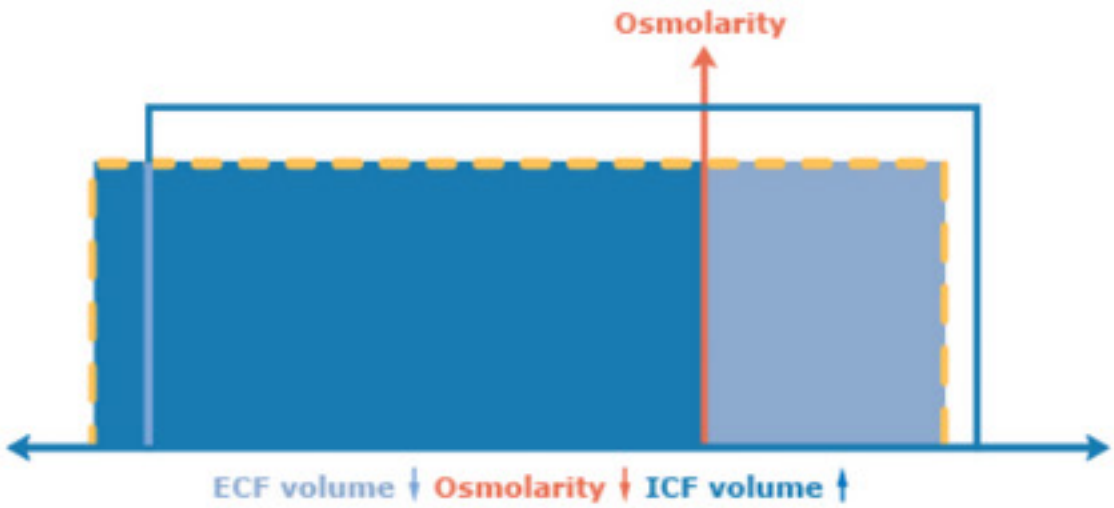
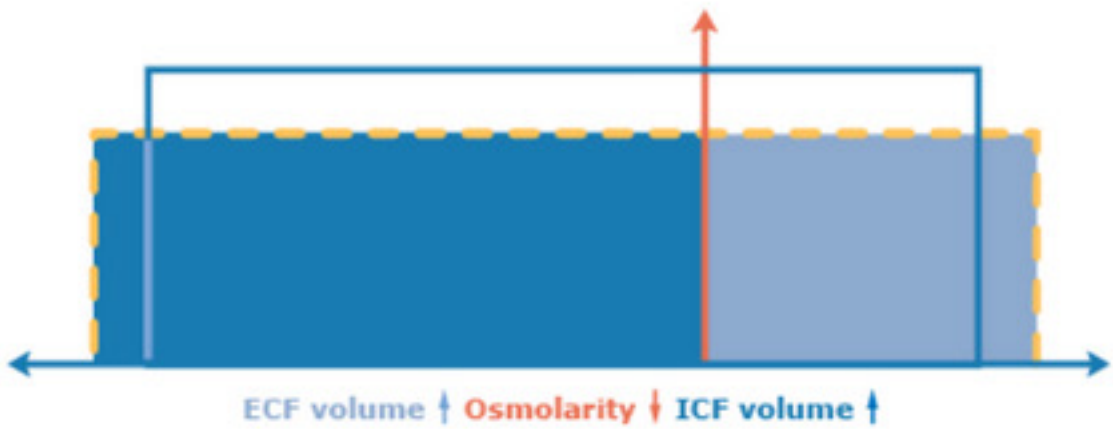
3. Loss of Hypertonic Fluid



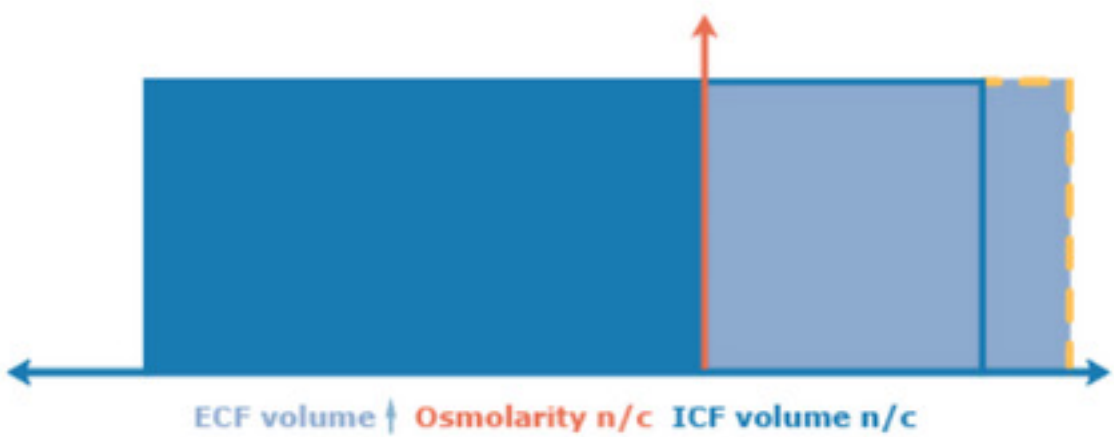
▲ **Figure 1–2.3C** Loss of Hypertonic Fluid

4. Gain of Hypotonic Fluid



▲ **Figure 1–2.3D** Gain of Hypotonic Fluid

5. Gain of Isotonic Fluid



▲ **Figure 1–2.3E** Gain of Isotonic Fluid

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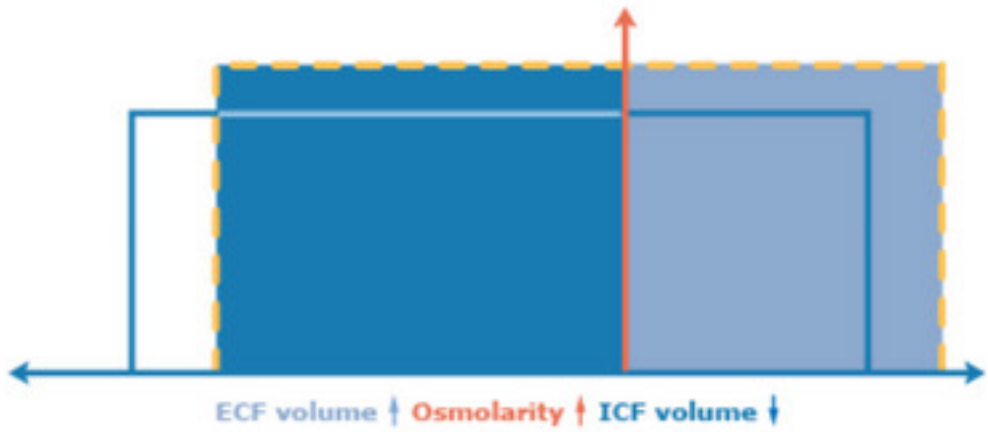
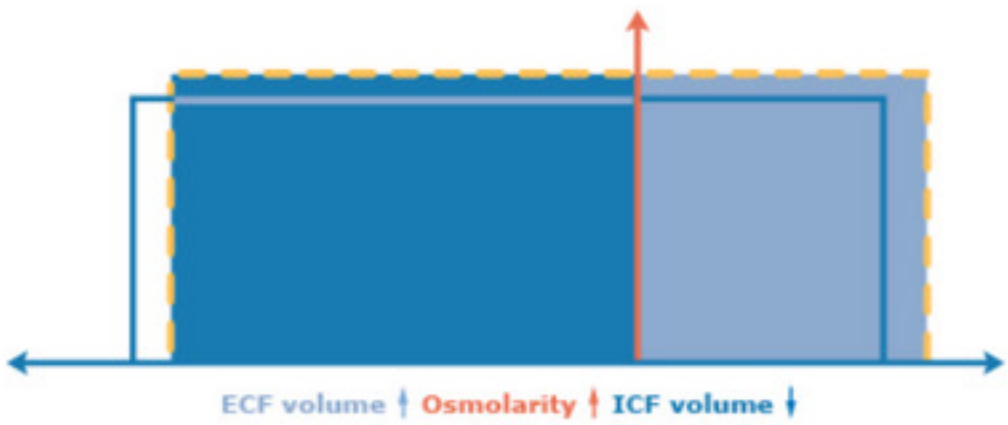
6. Gain of Hypertonic Fluid



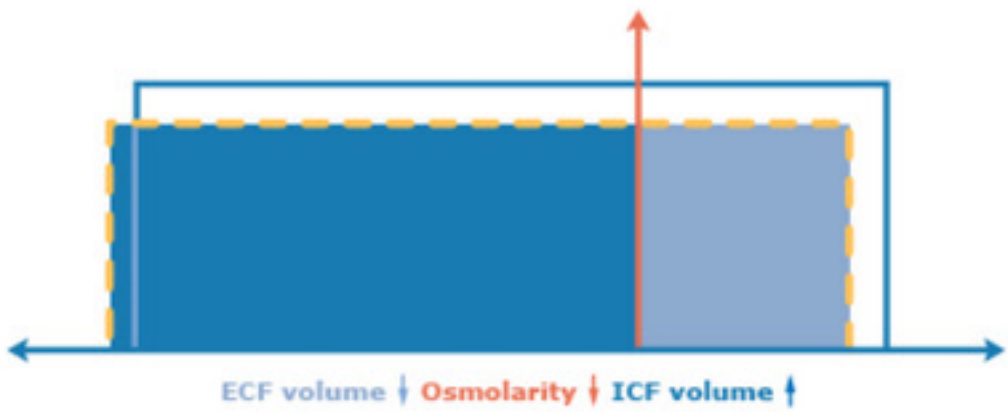
▲ **Figure 1–2.3F** Gain of Hypertonic Fluid

7. Gain of NaCl



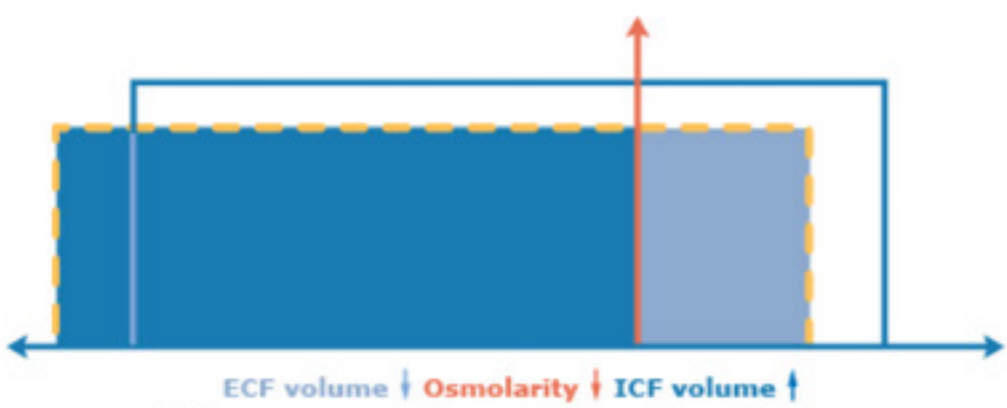
▲ **Figure 1–2.3G** Gain of NaCl

8. Loss of NaCl



▲ **Figure 1–2.3H** Loss of NaCl

2.4 Primary Adrenal Insufficiency



▲ **Figure 1–2.4 Primary Adrenal Insufficiency**

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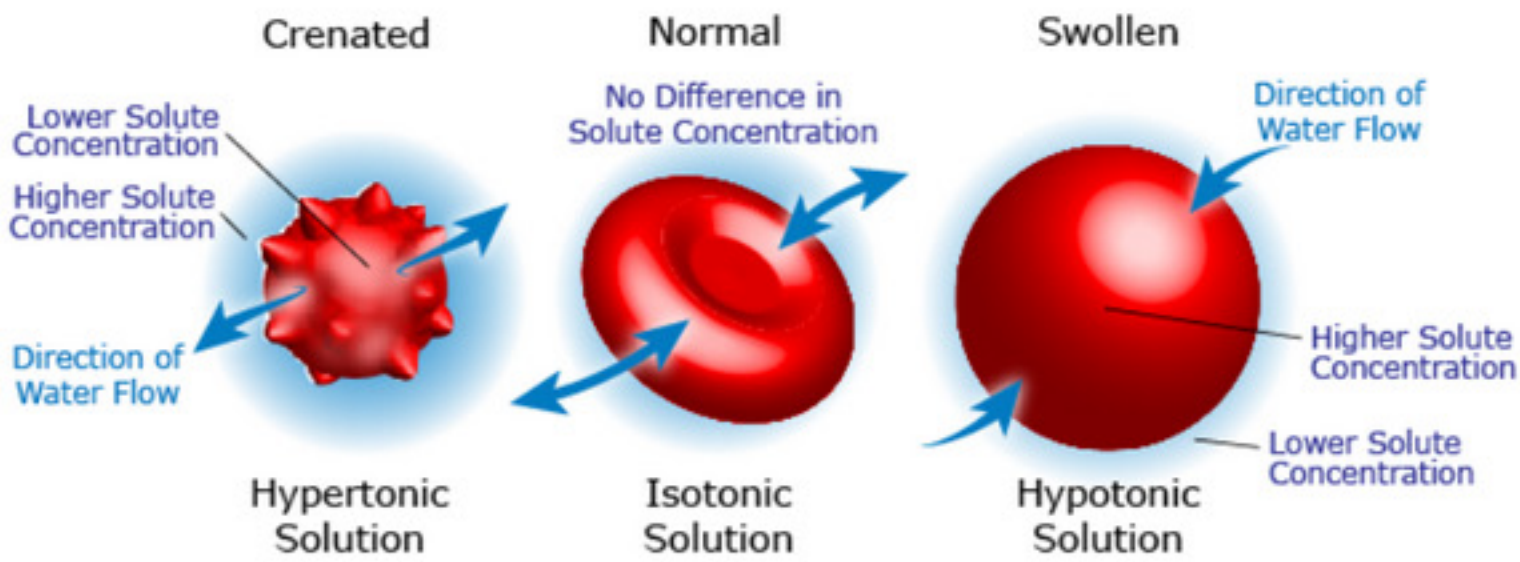
3 Tonicity Effects on the Red Blood Cell



▲ **Figure 1–3.0** Tonicity Effects on the Red Blood Cell

- **Isotonic solution** = 300 mOsm, no change
- **Hypotonic solution** < 300 mOsm, RBC swells
- **Hypertonic solution** > 300 mOsm, RBC shrinks

4 Interstitial Fluid (ISF) vs. Vascular Fluid (VF)

The ICF–ECF fluid exchange depends only on osmotic forces across the cell membrane. Any substance that cannot easily penetrate the membrane creates an osmotic effect. The osmotic effect of NaCl in the ECF is balanced by non-penetrating dissolved substances within the cell. Water equilibrates very quickly across the cell membrane, creating a stable environment.

The ISF–VF is continuously in a dynamic nonequilibrium state. Capillary forces are continuously moving water with dissolved substances across the capillary membranes. In many cases, water and dissolved substances are filtered across the arterial end of the capillary and reabsorbed across the venous end of the capillary. Any excess is removed via the lymphatic system. Capillary membranes are freely permeable to almost all dissolved substances within the plasma except the large proteins. Thus, it is the proteins, not sodium, that create the osmotic forces. The concentration of electrolytes in the plasma is essentially the same as the ISF.

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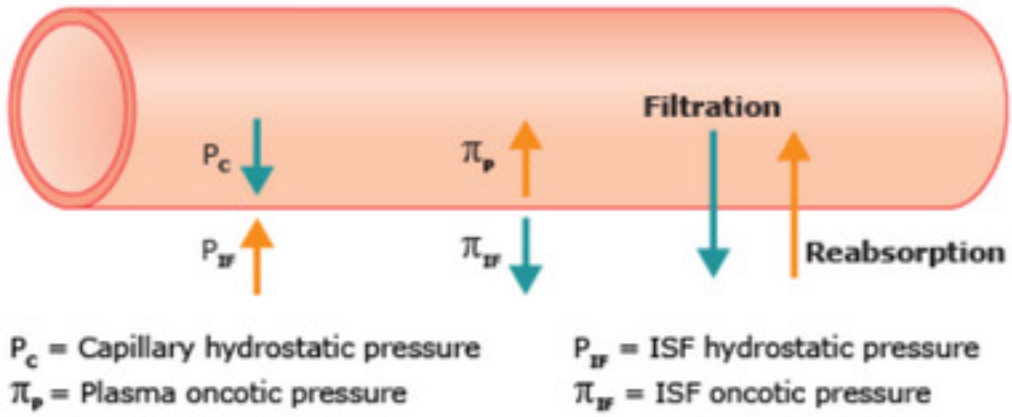
4.1 Forces Across the Capillary Membrane (Starling Forces)



▲ **Figure 1–4.1** Starling Forcs Across a Capillary Membrane

4.1.1 The Two Major Starling Forces

P_c—Capillary Hydrostatic Pressure This varies from tissue to tissue and decreases from the arterial to the venous end of the capillary.

- Filtration at the arterial end, and reabsorption at the venous end. An average value is approximately 25 mmHg.
- This is the main factor promoting filtration, and varies with the resistance of the arterioles.
- Dilation increases, and constriction decreases capillary pressure.
- There are no major resistance vessels between the capillaries and the veins.
- A rise in venous pressure is transmitted upstream into the capillaries.
- The main factor determining capillary hydrostatic pressure is the resistance of the arterioles.

π_p—Plasma Oncotic Pressure Is determined mainly by plasma albumins.

- Referred to as the *colloid* or *oncotic pressure* to distinguish it from the osmotic force acting across the cell membrane.
- An average value is approximately 28 mmHg. This is the main factor promoting reabsorption.
- Increased by any loss of fluid that does not contain protein, such as diarrhea, excessive sweating, vomiting, and diuresis without protein.
- Decreased by a gain of fluid that does not contain protein, such as tap water or saline infusion, but not whole blood or plasma (they contain protein). Cirrhosis and nephrotic syndrome.

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4.1.2 The Two Minor Starling Forces

P_{IF}—ISF Hydrostatic Pressure Generally close to zero and insignificant.

- In most tissues it may be slightly negative, and in encapsulated tissues it is slightly positive.
- The pleural pressure between the lung and chest wall is negative (−5 to −8 cmH_2O) but is not a factor promoting filtration under normal conditions.
- When excessively negative, it acts as a force promoting edema, as in respiratory distress syndrome.

π_{IF}—ISF Oncotic Pressure Proteins are continuously leaking into the ISF.

- They are removed along with other interstitial debris via the lymphatic system.
- Lymphatic capillaries have one-way valves that allow the ISF to enter but not return to the ISF.
- Lymphatic vessels contract, pumping the fluid toward to and eventually into the systemic veins, mainly via the thoracic duct.
- Normal oncotic ISF pressure is about 8 mmHg. It increases with removal or blockage of the lymphatic ducts, promoting lymphedema (nonpitting edema). Also rises with increased capillary permeability, as is seen with histamine and burn injuries.

4.2 Calculating Net Filtration Pressure:

$$\text{Net filtration pressure} = P_C - \pi_C - P_{IF}{*} + \pi_{IF}$$

Since factors that promote filtration are given a positive sign, and factors that promote reabsorption a negative sign, if the calculation is positive, there is net filtration; if negative, net reabsorption.

*This assumes a positive pressure. If it is a negative pressure, it is given a positive sign and promotes filtration.

Calculate a net filtration pressure:

P_C = 25 mmHg

π_C = 28 mmHg

P_{IF} = 2 mmHg

π_{IF} = 8 mmHg

Answer: +3 mmHg

+3 means a capillary net filtration. A negative sum suggests a net reabsorption.

The volume filtered per unit time (mL/min) also depends on a filtration coefficient (k_f). K_f depends on the capillary permeability and the available surface area.

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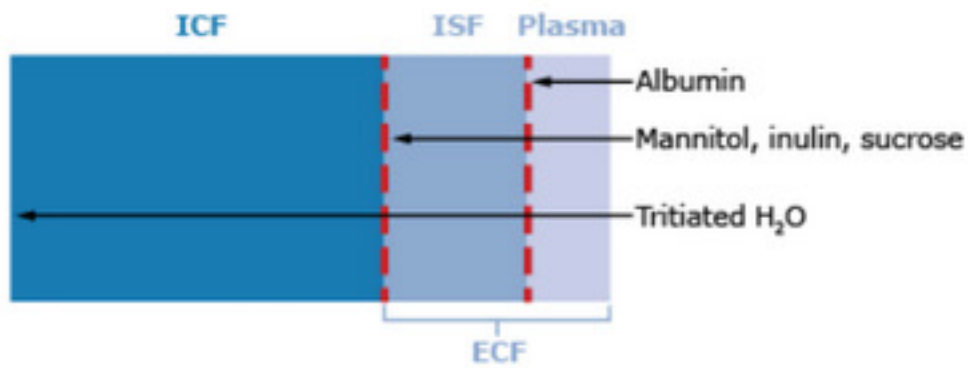
5 Tracers to Measure Specific Body Compartments

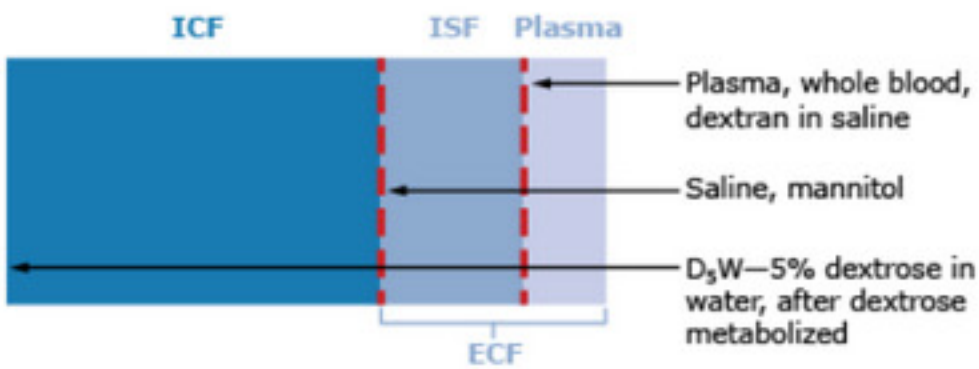


▲ **Figure 1–5.0** Distribution of Intravenous Tracers

All tracers first enter the plasma compartment.

Note: Tagged albumin measures the plasma volume. Blood volume measured by tagged RBCs.

6 Distribution of Intravenous Fluids



▲ **Figure 1–6.0** Distribution of Intravenous Fluids

Saline dilutes plasma proteins, causing an additional volume to distribute to the ISF (> 2/3 overall). Saline is a poor choice to expand the vascular compartment.

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7 Edema

7.1 Systemic Edema

Edema is usually a reference to the interstitial accumulation of fluid, but there can be an intracellular accumulation as well. Hyponatremia, ischemia, and inflammation can shift fluid to the intracellular compartment.

Two separate sets of conditions are responsible for the development of interstitial edema.

1. The first is a two-stage process:

Stage 1: There is initially a change in the Starling forces that favor filtration to the interstitium. This can be:

- $P_C \uparrow$
- $\pi_C \downarrow$
- Filtration coefficient $\uparrow$
- $\pi_{IF} \uparrow$

$\pi_{IF} \uparrow$ caused by a blockage or removal of lymphatic vessel causes lymphedema, a nonpitting edema that does not respond to diuretics.

Stage 2: The second stage results from the fluid shift and an under-fill of the vascular compartment. This activates the renin-angiotensin-aldosterone system to retain sodium and water, refilling the vascular compartment and continuing the fluid shift to the interstitium.

2. The second type of interstitial edema originates as an over-fill of the vascular compartment. One example is low-output heart failure that activates the renin-angiotensin-aldosterone system to over-fill the system. A second example is nephretic syndrome, characterized by a dramatic decrease in GFR and the retention of fluid. This often results in hypertension as well as long-term edema.

7.2 Pulmonary Edema

Pulmonary circulation is uniquely different. There is still a net filtration to the interstitium, but this fluid must be prevented from entering the alveoli. The high concentration of interstitial protein and the alveolar membrane's impermeability to this protein maintain an osmotic force that keeps the alveoli dry.

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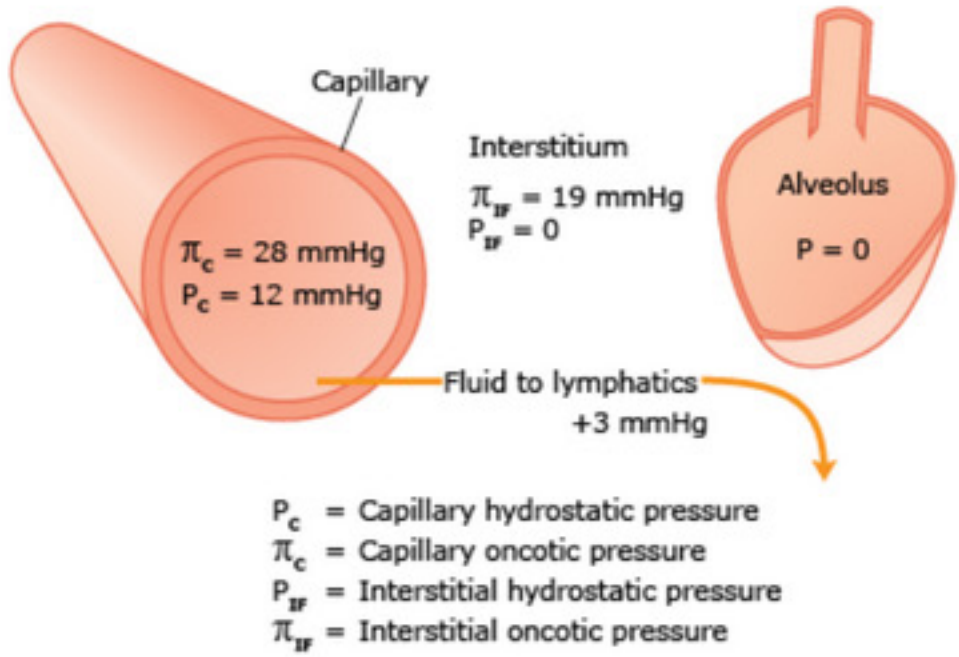

▲ **Figure 1–7.2** Starling Forces Across a Pulmonary Capillary

7.2.1 Cardiogenic (Starling Forces Imbalance)

- Increased capillary hydrostatic pressure secondary to elevated pulmonary venous pressure caused by left heart dysfunction.
- Accentuated by low plasma proteins.
- Transduction of fluid first to the interstitium; then to the alveoli.
- Initial washout of interstitial protein is a protective feature.
- Dyspnea can be reduced or relieved with an upright posture.
- Treatment centers on reducing left atrial pressure.

7.2.2 Acute Lung Injury (ARDS)

- Caused by a primary injury to the alveolar epithelium.
- Direct injury due to gastric aspirations.
- Indirect due to injury to capillary endothelium (sepsis).
- Fluid and protein accumulate within the alveoli.
- Alveolar protein compromises surfactant's function.
- Atelectasis and shunting of blood.
- Layered sheets of pink proteinaceous substances form in the alveoli (*hyaline membranes*).

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Unit 2

Cell Physiology

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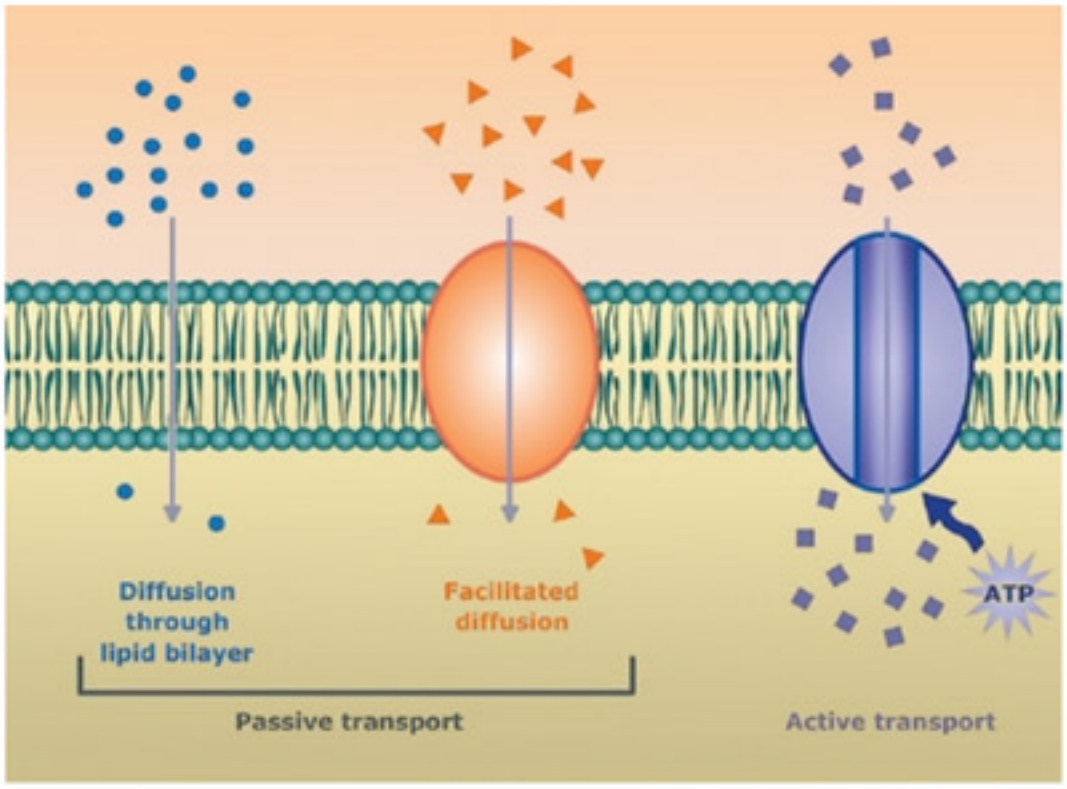
1 Diffusion (Simple Diffusion)



▲ **Figure 2–1.0** Mechanisms of Membrane Transport

A passive non-protein mediated transport across cell membranes. Lipid-soluble substances readily diffuse through the membrane structure. Lipid insoluble (water soluble) substances can diffuse through pores and channels. If a substance can easily penetrate a membrane, the main transport mechanism is simple diffusion.

1.1 Fick Law of Diffusion

$$J \propto \frac{A}{T} \times S \times \Delta P$$

- J = rate of diffusion
- A = surface area available for diffusion
- T = thickness of the membrane system
- S = solubility in the membrane or index of how easily the molecule penetrates the membrane (conductance)
- Δ P = the concentration gradient across the membrane. This applies to a non-charged molecule. With a charged ion, the net force depends on both the concentration gradient and the electrical gradient.

With simple diffusion, each substance diffuses independently. There is no direct interaction among the molecules.

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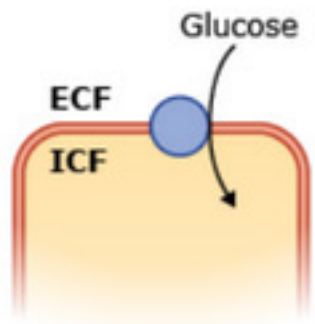
2 Carrier-Mediated Transport

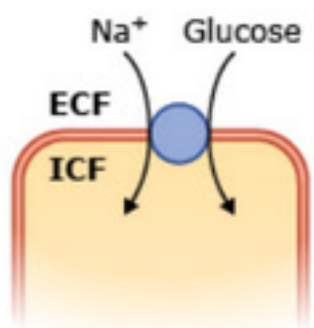
Protein carriers are generally present only for molecules that cannot easily penetrate the membrane. If it can easily penetrate, it will diffuse.

- **Uniport:** Single molecule transported: glucose-transported into skeletal muscle.



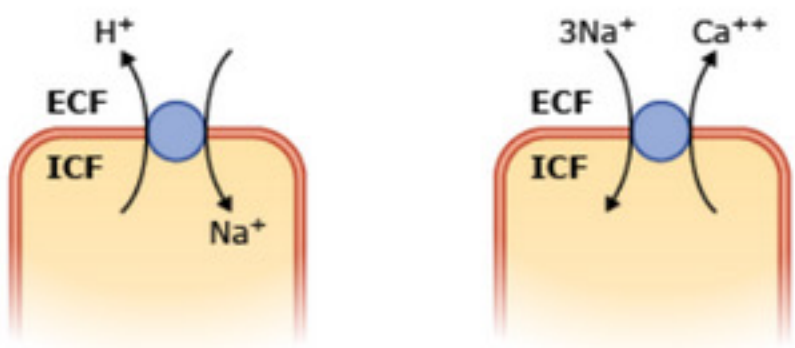
▲ **Figure 2–2.0A** Uniport Membrane Transport

- **Symport:** Two or more molecules coupled in the same direction, as in Na^+, glucose in the proximal tubule of the kidney and small intestine. In some cases, 1 and in other cases 2 Na^+ transported with a single glucose molecule. The conformational change for transport will not occur unless both Na^+ and glucose are attached to the transporter.



▲ **Figure 2–2.0B** Symport Membrane Transport

- **Antiport:** Two or more molecules coupled in opposite directions, as in Na^+, H^+ transport in the proximal tubule of the kidney, Na^+ and Ca^{++} transport across cardiac ventricular cells. For the latter, 3 Na^+ are transported for each Ca^{++}.



▲ **Figure 2–2.0C** Antiport Membrane Transport

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In all of the above examples, the transport proteins do not have ATPase activity. As such, transport is driven by the electro-chemical gradients. In most cases, if the gradients are altered, the transport can reverse. For example, in the cardiac ventricular muscle, the net inward force of the 3 Na^+ pumps the Ca^{++} from inside to outside the cell. Digitalis increases the intracellular Na^+, reducing the inward net force on Na^+. If the inward net force on Ca^{++} is now greater than the inward net force on Na^+, the inward movement of Ca^{++} pumps out the Na^+.

Protein mediated transport exhibits saturation dynamics. The transport rate (e.g., mg/min) when the carriers are saturated is referred to as the *transport maximum* (T_m). T_m is directly proportional to the number of available transporters. There is specificity and competition for the carriers: Glucose transporters transport either glucose or galactose, but not sucrose.

2.1 Facilitated Transport *(Facilitated Diffusion)*

A passive process where the net movement is down the electrochemical gradient.

2.2 Active Transport

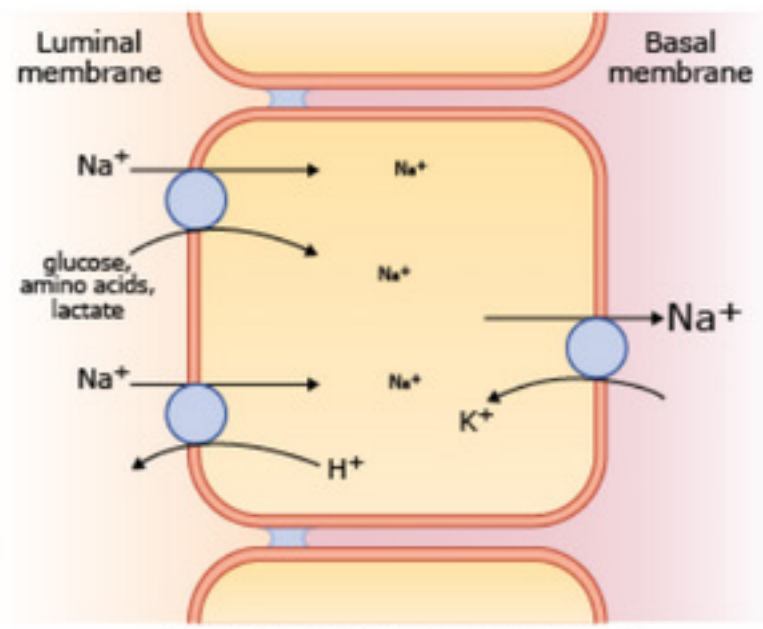
Utilizes ATP as a source of energy. Thus, movement can be against the electrochemical gradient.

2.2.1 Primary Active Transport

The transporting protein has ATPase activity. Directly uses ATP as a source of energy. The Na/K-ATPase pump has three binding sites for Na^+ on the intracellular domain and two binding sites for K^+ on the extracellular domain. There is a net transfer of charge, pump is electrogenic.

2.2.2 Secondary Active Transport

Depends indirectly on the energy supplied by the Na/K-ATPase pump. The protein transporter functions by transporting sodium into the cell. If the substrate follows the sodium, it is symport. If the substrate moves in the opposite direction to sodium, it is antiport.



▲ **Figure 2–2.2** Secondary Active Transport in Proximal Tubule of Kidney

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2.2.3 Summary

Primary active transport of sodium on the basal membrane maintains the large ECF/ICF Na^+ gradient. The secondary active transport at the luminal membrane is powered by that Na^+ gradient.

2.2.4 General Characteristics

- Sodium gradient powers the uptake.
- Luminal sodium (gradient) stimulates the uptake of substrate.
- Luminal substrate stimulates the uptake of sodium.
- Sodium/substrate coupling required for uptake.
- Either symport or antiport.
- Dependent on the Na/K-ATPase pump.

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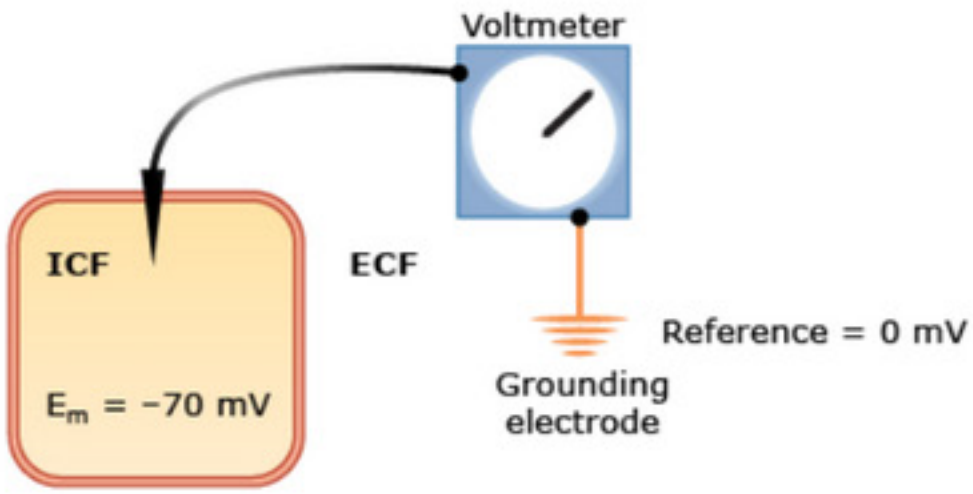
1 Introduction

Voltage is a potential difference between two points. *Membrane potential* is the voltage difference across the cell membrane. It is measured using an indifferent electrode (grounding electrode) in the ECF (0 mV) and a measuring electrode placed through the cell membrane into the ICF.



▲ **Figure 3–1.0** Measurement of Membrane Potential

1.1 Voltage Across Cell Membrane

Under resting conditions, the voltage difference across the cell membrane of many neurons is about −70 mV (others up to −90 mV). If the membrane potential is originally 0 mV (no voltage across the membrane), only 1/200,000,000 of the positive charges inside the cell would need to be removed to create ICF of −70 mV.

- This also means, for example, that when some sodium channels are opened in the membrane, and Na^+ diffuses into the cell, only positive charges are moving. Not enough sodium enters the cell to significantly affect the ICF or ECF concentration of sodium.
- This applies to all the ions considered except Ca^{++}. The normal intracellular free Ca^{++} is close to zero.
- Increasing the membrane conductance to Ca^{++} allows an influx and a rise in the intracellular free Ca^{++}.
- This, in many cases, is an intracellular signal that triggers a cascade of events.
- This can be the release of transmitter at the synaptic junction or the release of additional Ca^{++} from the sarcoplasmic reticulum of cardiac muscle cells.

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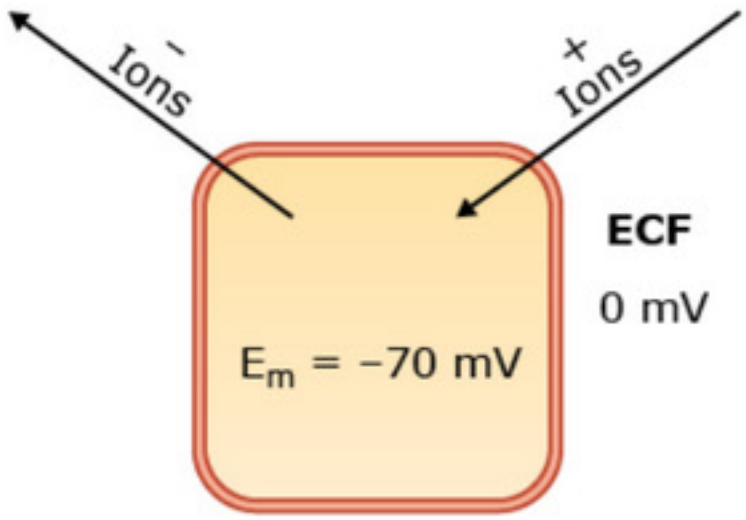
2 Membrane Potential vs. Equilibrium Potential

Understanding the forces acting on an ion and how to relate the membrane potential to an ion's equilibrium potential is the basis of understanding ions diffusing through channels.

The membrane potential is an electrical force acting on all charged particles, as shown in the figure.



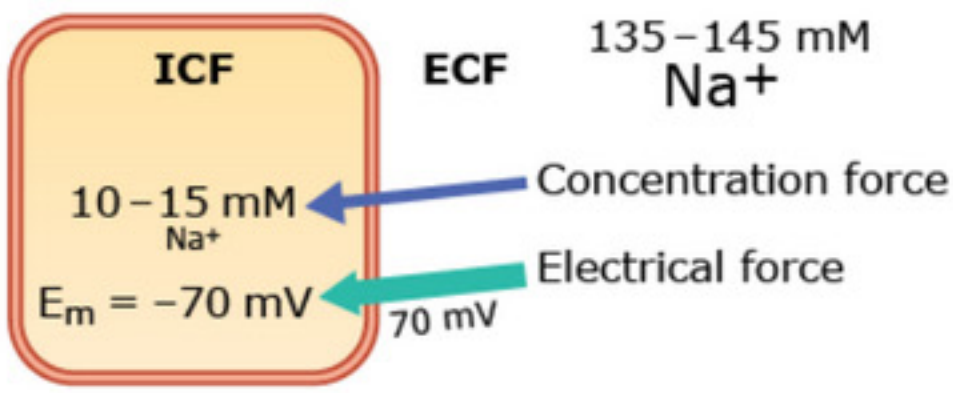
▲ **Figure 3–2.0** Electrical Forces on Ions

2.1 Net Force

With charged particles, two separate forces must be considered:

1. Electrical Force
2. Concentration Force

These two forces combine (based on direction) to exert the net force on the ion. Consider the forces acting on sodium under resting conditions.



▲ **Figure 3–2.1A** Concentration and Electrical Forces on Sodium

- The concentration and electrical forces are directed inward, and the net force is the sum of the two.
- If Na^+ channels are opened, positive charges diffuse into the cell and the membrane potential becomes more positive; it moves toward 0 mV.

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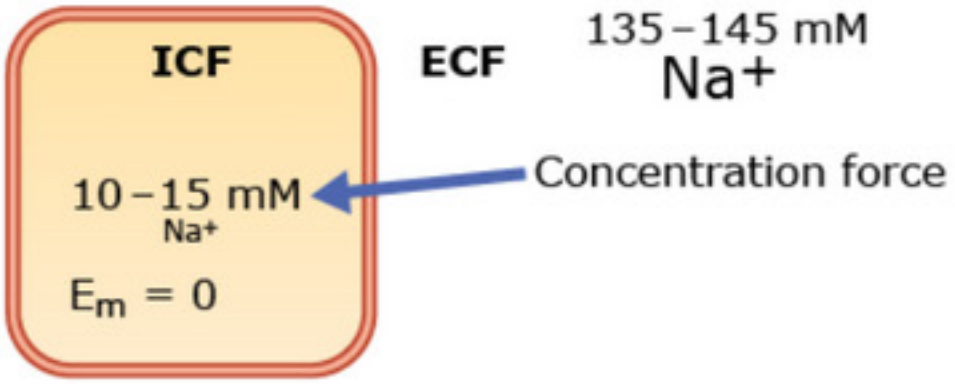


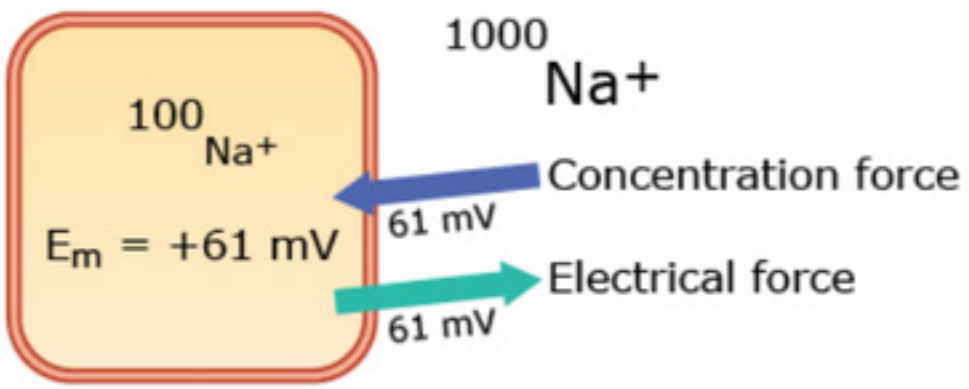
▲ **Figure 3–2.1B** Concentration Force on Sodium, Depolarized Cell

- At 0 mV, there is only the concentration force directed inward, and continued diffusion of Na^+ inward causes E_m to be positive.
- If the membrane potential becomes +45 mV, the inward diffusion of Na^+ stops because the +45 mV force directed outward balances the inward concentration force. Not enough ions flow to significantly change concentrations or the concentration force.
- The membrane potential required to balance the concentration force is referred to as the *equilibrium potential* for that ion.
- For sodium under the conditions stated, it is +45 mV. This number can be calculated from the Nernst equation.

$$E_x = \pm 61 \times \log \frac{\text{concentration inside}}{\text{concentration outside}}$$

- The unknowns are the ECF and the ICF concentrations of the ion. In other words, we put in the concentration force and the equation calculates the membrane potential necessary to balance this force. If the ECF or the ICF concentration changes, the equilibrium potential changes.

  For example, with an ECF Na^+ concentration of 1,000 mM, and the ICF concentration of 100 mM, the equilibrium potential is +61 mV. The absolute number is the concentration force in mV.



▲ **Figure 3–2.1C** Hypothetical Example of Sodium at Equilibrium

Equal but opposite forces equals equilibrium.

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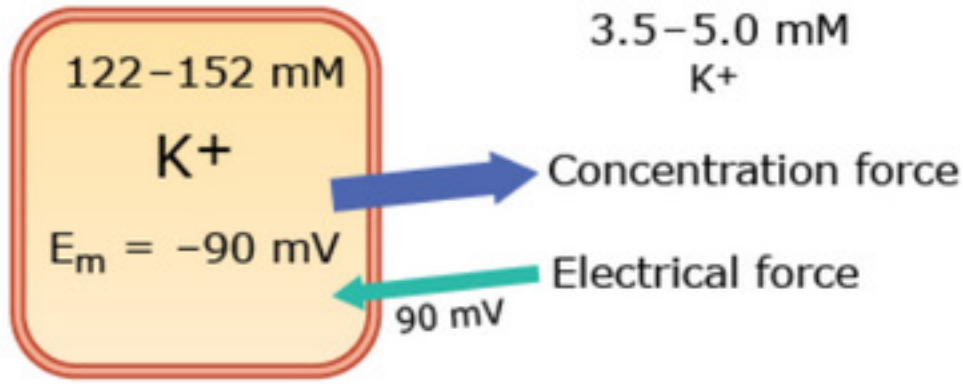
2.2 Potassium

Consider the situation for potassium:

If we calculate the equilibrium potential for K^+, it is approximately (−102mV). This is the magnitude of the concentration force. If there is no ionic movement except K^+ through open channels in the membrane, there would be a slow efflux (greater concentration force). When this occurs, the membrane potential becomes more negative. K^+ efflux stops when E_m reached −102 mV. The outward 102 concentration force is balanced by the electrical 102 force (all in mV units).



▲ **Figure 3–2.2** Concentration and Electrical Forces on Potassium

2.3 Important Conclusions

The cell's membrane potential and an ion's equilibrium potential calculated from the Nernst equation lead to the following conclusions:

- If the membrane potential and the ion's equilibrium potential are the same, the ion is at equilibrium (net force is zero).
- If the membrane potential and the ion's equilibrium are different, there is a net force across the membrane.
- The difference between the ion's equilibrium potential and the membrane potential is the net force across the membrane.
- As the ion diffuses through channels and the membrane potential approaches the ion's equilibrium potential, the net force decreases.
- The ion always diffuses in a direction to change the membrane toward the ion's equilibrium potential.

2.4 Theoretical Situations

- Situation A

  E_m = −70 mV

  E_{S^-} = −90 mV Equilibrium potential for ion S−

  1. Is the ion at equilibrium? *Answer:* No

  2. What is the net force across the membrane?
  Answer: 20 mV. (−70) − (−90) = absolute difference of 20

  3. If channels are open, is it an influx or an efflux?
  Answer: Influx. For a negative ion to make the ICF more negative, it must diffuse into the cell.

- Situation B

  E_m = −70 mV

  E_{R^-} = +20 mV

  1. Is the ion at equilibrium? *Answer:* No

  2. What is the net force on the ion?
  Answer: 90 mV. −70 − (+20) = 90

  3. If channels are open, is it an influx or an efflux?
  Answer: Efflux. For a negative ion to make the ICF more positive, it must diffuse out of the cell.

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3 Membrane Conductance

In reference to an ion, this term is giving information on only the status of membrane channels. Zero conductance to an ion means that there are no channels for that ion or they are closed.

- Conductance ↑, channels are opening.
- Conductance ↓, channels are closing.

The rate at which charges are diffusing through channels depends on both the membrane conductance to that ion and the net force across the membrane.

3.1 Channels

We can classify channels into three main groups:

1. **Voltage-Gated Channels:** respond to a voltage change across the membrane, usually a depolarization. A depolarization may cause an open channel to close or a closed channel to open. Voltage-gated sodium channels open (activate) with a depolarization.
2. **Ligand-Gated Channels:** do not respond to a voltage change. Instead, they have a receptor designed to bind a specific molecule. The receptor-molecule complex can open or, in some cases, close the channel. At the neuromuscular junction, the postsynaptic membrane has ligand-gated channels that bind acetylcholine.
3. **Ungated Channels:** always open in the membrane. Many cells, such as neurons, possess ungated potassium channels in the membrane. Since at rest, potassium is close to but not at equilibrium, there will be a net diffusion (efflux). These channels are often referred to as *potassium leak channels.* To maintain the steady-state at rest, there must be open potassium leak channels. They may be ungated, open voltage-gated, or open ligand-gated.

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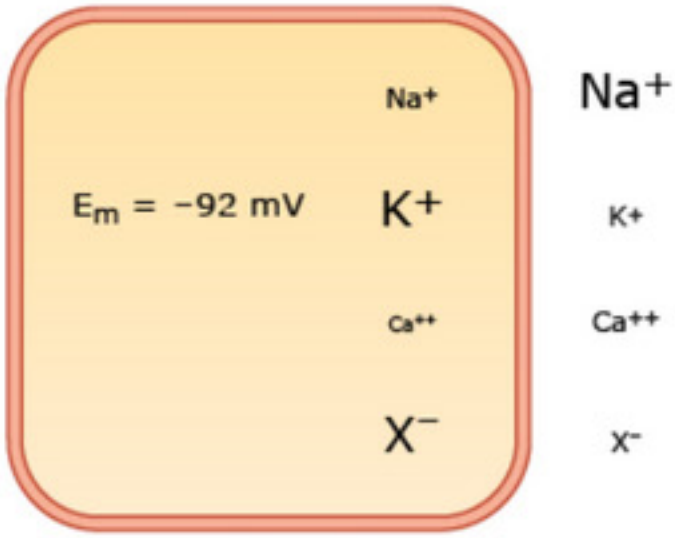
4 Characteristics of a Typical Cell



▲ **Figure 3–4.0** Resting Forces on Important Ions

E_{Na+} = +41 mV
E_{K+} = −102 mV
E_{Ca++} = +140 mV
E_{X^-} = −92 mV

4.1 Sodium

- Net force on sodium: −92 − (+41) = 133 mV directed inward.
- Conductance close to zero.
- ↑ conductance: influx of sodium, cell depolarizes, but not beyond +41 mV.
- A change in extracellular concentration affects cell size, but not the resting membrane potential.

4.2 Potassium

- Close to equilibrium: −92 − (−102) = 10 mV.
- Efflux through leak channels.
- ↑ conductance ↑ efflux and hyperpolarization, but not beyond −102 mV.
- ↑ ECF potassium (hyperkalemia) – depolarization.
- ↓ ECF potassium (hypokalemia) – hyperpolarization.

A cell's resting membrane potential is not sensitive to extracellular sodium, but is very sensitive to extracellular potassium.

4.3 Calcium

- Very large net force: −92 − (+140) = 232 mV.
- Conductance close to zero.
- ↑ conductance – influx – depolarization – ↑ intracellular free calcium.
- ↓ ECF Ca^{++} ↑ sensitivity of neuron voltage-gated sodium channels.

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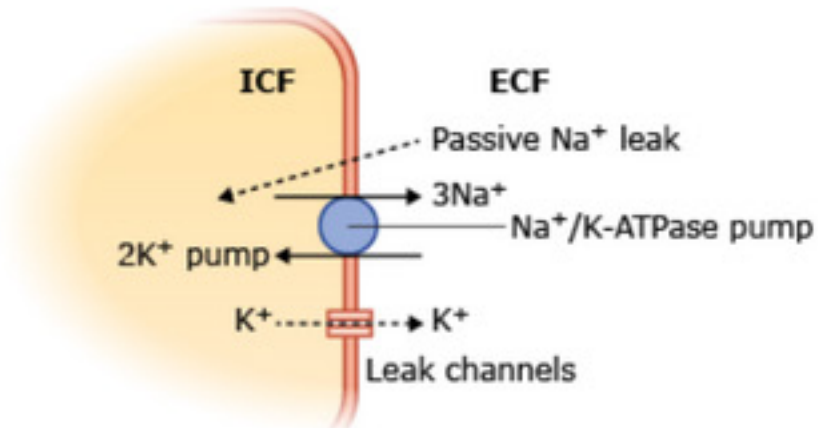
4.4 Hypothetical Ion X^-

- Equilibrium—net force zero.
- ↑ or ↓ conductance will not change the membrane potential.
- If membrane potential changes, X^- diffuses, if channels open, to bring it back toward −92 mV.
- $E_m = E_{x^-}$; this may have developed because the membrane has a high conductance to X^-.

Steady-state Sodium and Potassium Dynamics:



▲ **Figure 3–4.4** Steady-State Sodium and Potassium Dynamics

- Sodium is always passively leaking into the cell.
- Na/K-ATPase pump removes the sodium and maintains low ICF sodium.
- Sodium diffusing in = sodium pumped out.
- Potassium is always being pumped into the cell.
- Potassium is always diffusing out through the leak channels.
- Potassium pumped in = potassium diffusing out.

Ischemia and the Failure of the Na/K-ATPase pump:

- Inward diffusion of sodium depolarizes the cell.
- Water diffuses into the cell and the cell swells.
- Potassium diffuses out of the cell, ↑ ECF potassium locally.

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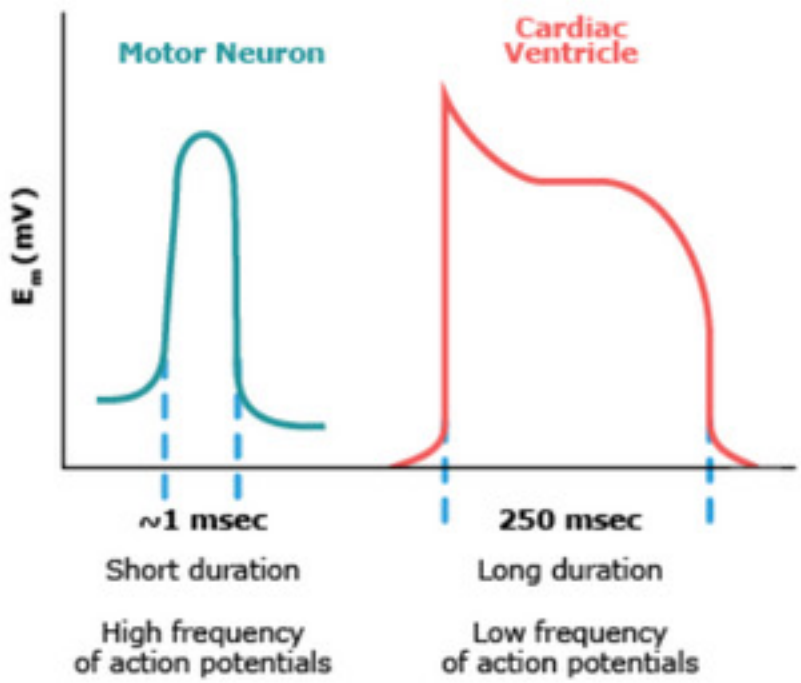
1 Introduction

There are two completely different action potentials: the neuron action potential (discussed in this chapter), and the cardiac ventricular action potential (discussed in Chapter 5). Some major differences are illustrated in the following figure. The action potential of a skeletal muscle cell is almost identical to that of a neuron.



▲ **Figure 4–1.0** Neuron vs. Cardiac Ventricular Action Potential

The action potential is an "all-or-none" response. Once the initiating stimulus reaches threshold and an action potential is generated, it is conducted with the same size and shape along the entire length of the neuron, usually from the axon hillock to the nerve terminals. The size of the initiating stimulus, on the other hand, depends on stimulus strength, and the response decreases in magnitude exponentially from the point of origin.

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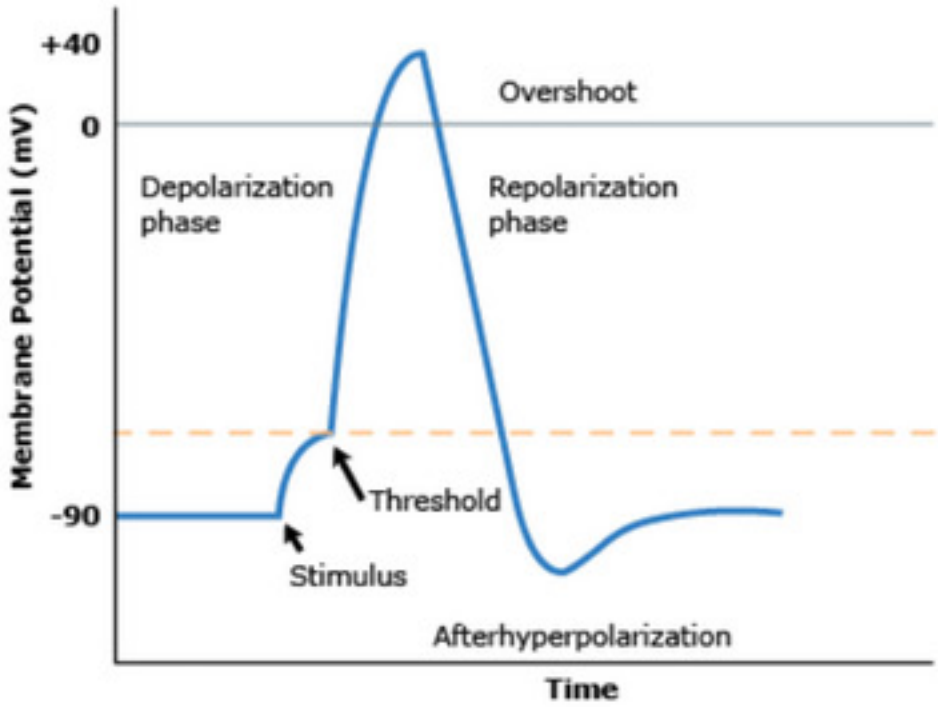
2 Components of the Neuron Action Potential



▲ **Figure 4–2.0** Phases of the Neuron Action Potential

The action potential has three phases; *depolarization*, *repolarization* and *afterhyperpolarization*. We will focus on the first two. Notice that at the end of the depolarizing spike, the membrane potential is positive (overshoot).

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3 Membrane Channels

3.1 Potassium Leak Channels

Allow the potassium efflux under resting conditions. This efflux continues during the action potential.

3.2 Voltage-Gated Sodium Channels

Have two voltage-sensitive gates. At rest, the activation gate (m gate) is closed, and the inactivation gate (h gate) is open. Both gates respond to a depolarization. The activation gate quickly opens, allowing a sodium influx. The inactivation gate responds a little more slowly and closes, terminating the sodium influx. These channels activate quickly and inactivate quickly (terminate sodium influx). They are often referred to as the *fast channel* or the "fast" voltage-gated channel. The inactivation gate reopens at the end of repolarization after the activation gate closes. The resting state is sometimes referred to as the closed state. If the cell does not repolarize, the channel is in a nonfunctional state (inactivated state) and cannot establish an open (activated) state in response to another stimulus.

Functional fast channels are absolutely required for the development of action potentials in neurons and skeletal muscle.

3.3 Voltage-Gated Potassium Channels

Have only one voltage-sensitive gate. It is closed under resting conditions. Depolarization signals these gates to slowly open. Repolarization signals these gates to close.

Summary: The fast channels activate fast and inactivate fast. They peak open early in the action potential during depolarization. The voltage-gated potassium channels open slowly and close slowly, peaking open later in the action potential during repolarization.

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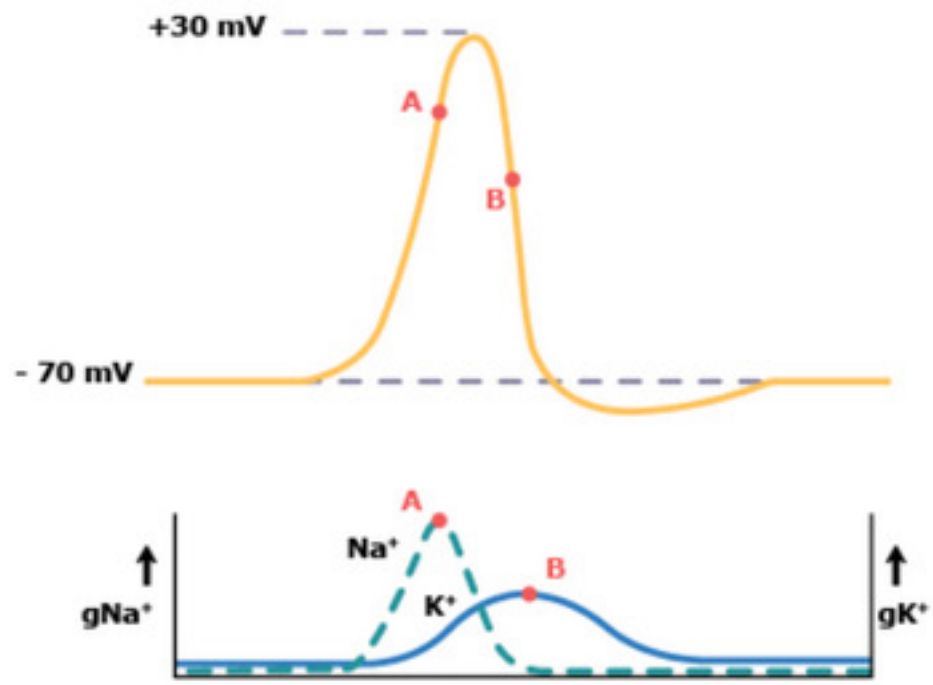
4 Voltage vs. Conduction Changes During the Action Potential

Notice that in the following figure, sodium conductance peaks just before the peak of the action potential, and potassium conductance peaks later, at about the midpoint of repolarization.



▲ **Figure 4–4.0** Sodium and Potassium Conductance Changes During the Action Potential

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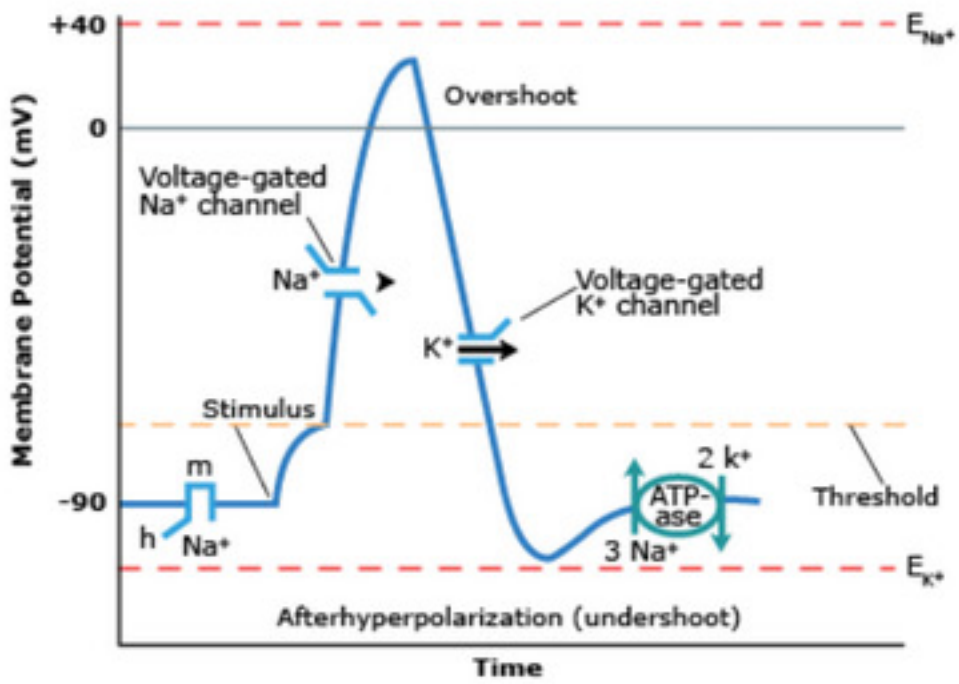
5 The Overall Response



▲ **Figure 4–5.0** Overall Dynamics During the Neuron Action Potential

- Initial depolarizing stimulus activates the fast channels.
- Sodium influx generates the depolarization phase.
- Sodium channels inactivate at about the peak of the action potential.
- Peak of the action potential: small force on sodium, large force on potassium.
- Slowly opening voltage-gated potassium channels open and peak about the midpoint of repolarization.
- Potassium efflux generates repolarization.
- Potassium channels do not fully close until after repolarization; afterhyperpolarization.
- Original sodium-potassium gradients established by the Na^+/K^+-ATPase pump.

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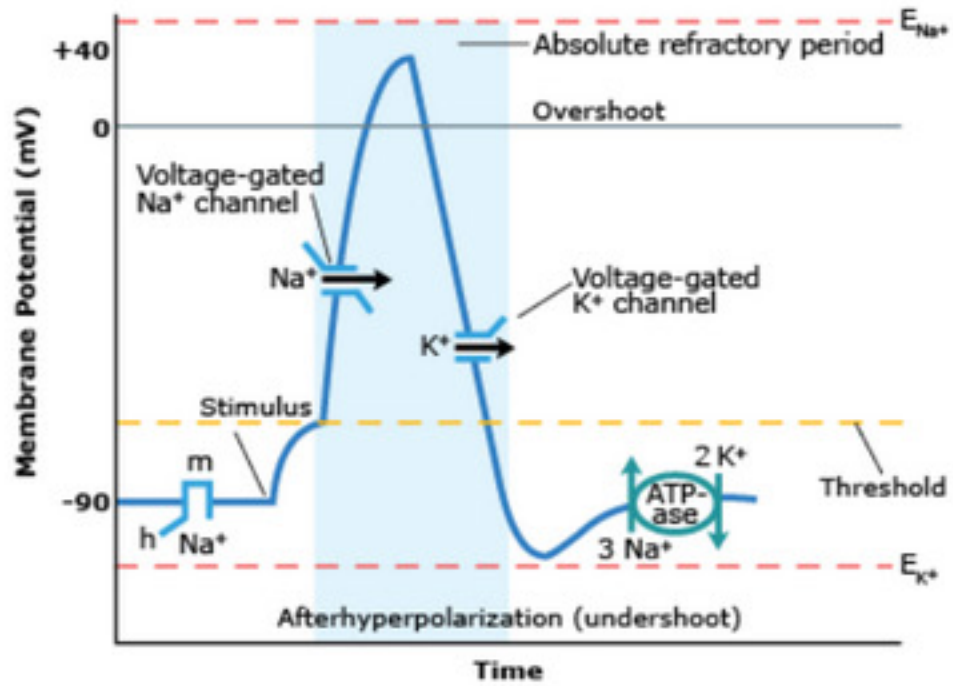
6 Absolute Refractory Period = Functional Refractory Period

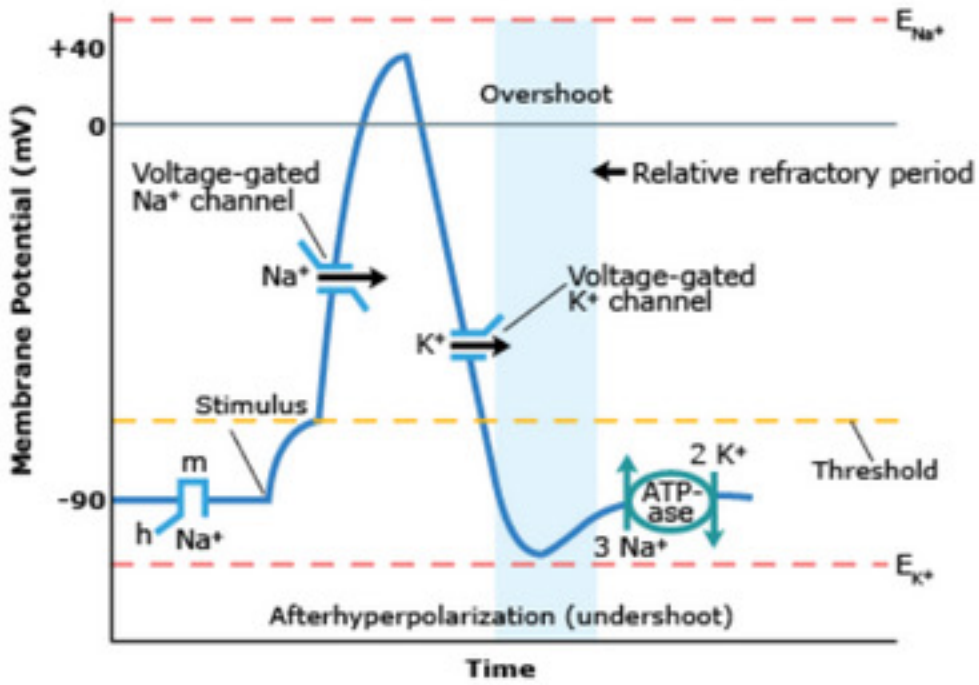
During this period, a second action potential cannot be generated, no matter how strong the stimulus. The inactivation gate is closed. It begins at threshold and continues until the cell has almost completely repolarized.



▲ **Figure 4–6.0** The Absolute Refractory Period

6.1 Relative Refractory Period

This is a period immediately following the absolute refractory period when a greater than normal stimulus is required to initiate an action potential. This is probably due to the fact that not all of the fast channels have been reactivated, as well as the slow return of potassium conductance to the resting level.



▲ **Figure 4–6.1** The Relative Refractory Period

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7 Factors Determining the Velocity of the Action Potential

7.1 Action Potential Factors

- The larger the amplitude, the greater the velocity.
- The greater the rate of depolarization, the greater the velocity.

7.2 Neuron Factors

- The greater the diameter, the greater the velocity.
- The greater the myelination, the greater the velocity.

Myelin increases the electrical resistance of the membrane. In heavily myelinated neurons, the action potential is conducted from one node of Ranvier to the next. It is at the nodes that the membrane contains the voltage-gated channels. In demyelinated diseases (Guillain-Barré, multiple sclerosis), there is a loss of membrane resistance between the nodes. More current leaks to ground, decreasing the magnitude of the stimulus received at the next node.

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1 Introduction

Synaptic transmission can be either chemical or electrical. It is now known that throughout the central nervous system, there are both chemical and electrical synapses.

1.1 Electrical Synapses (Gap Junctions)

- Low-resistance pathways between cells that allow direct current flow.
- Very fast and bidirectional.

1.2 Chemical Synapses

- Depend on transmitter release
- Operate in only one direction
- Synaptic delay

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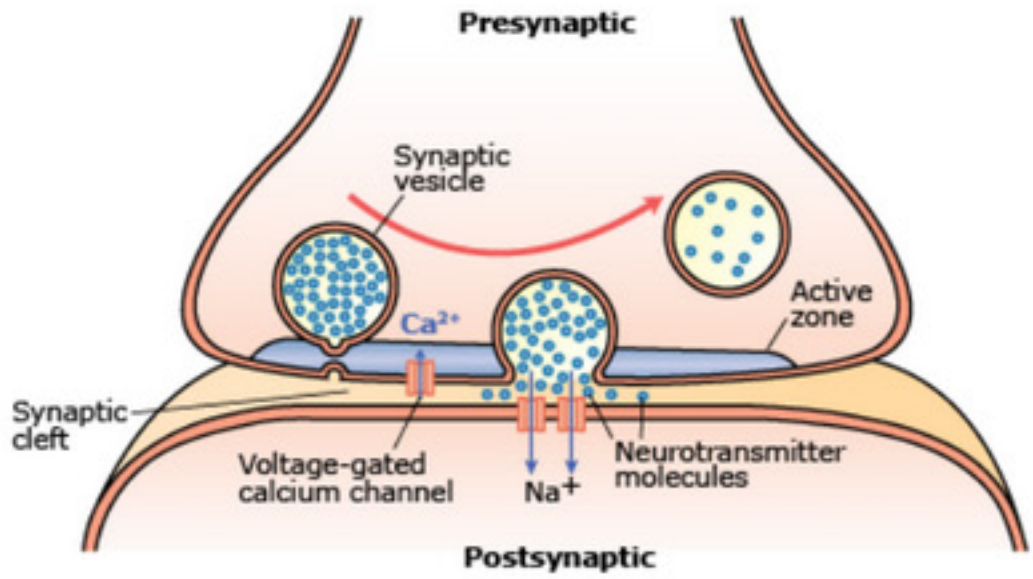
2 The Neuromuscular Junction



▲ **Figure 5–2.0** Synaptic Transmission at the Neuromuscular Junction

- Neuronal action potential terminates on the active region of the presynaptic membrane.
- Activation of voltage-gated Ca^{++} channels on the active presynaptic membrane.
- Influx of Ca^{++} causes a local ↑ in ICF free Ca^{++} adjacent to presynaptic membrane.
- Ca^{++} triggers the fusion of transmitter (ACH) containing vesicles with the presynaptic membrane.
- Quantal release of ACH into the synaptic cleft.
- Diffusion of ACH to the postsynaptic membrane receptors. Receptor and ion channel are part of the same molecule.
- Ligand–gated channel opens.
- ↑ conductance of postsynaptic membrane (Na^+ and K^+).
- Main current flow is an influx of Na^+, not an efflux of K^+ (reversal potential 0 mV).
- Depolarization of postsynaptic membrane (EPP end-plate potential).
- Local current flow to sarcolemma outside the synaptic region.
- Depolarization of membrane significantly beyond threshold.
- Generates an action potential that spreads not only across the surface sarcolemma, but down the T-tubular membranes.
- Enzymatic destruction of ACH by acetylcholinesterase terminates transmitter action, and ligand-gated channels close.

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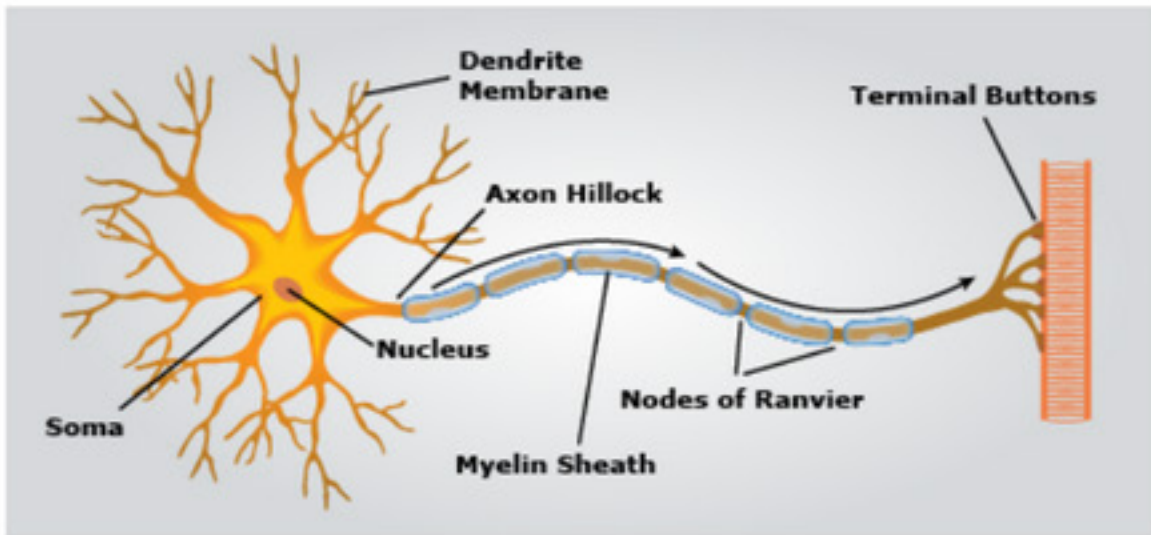
3 Neuron–Neuron Synapses



▲ **Figure 5–3.0** Schematic of a Nerve Cell

- Synaptic connections are on the cell body and the dendritic membranes.
- Excitatory transmitter depolarizes the postsynaptic membrane (EPSP).
- Inhibitory transmitter hyperpolarizes the postsynaptic membrane (IPSP).
- Local current flow toward the axon hillock, where there is a high density of voltage-gated channels.
- Depolarization, if to threshold at the axon hillock, initiates an action potential that travels down the axon to the nerve terminals, where transmitter is released.

3.1 Excitatory Postsynaptic Potentials (EPSP)

- Transmitters depolarize.
- Increased conductance of the postsynaptic membrane to both Na^+ and K^+.
- Main current flow is an influx of Na^+.
- Transmitters include acetylcholine, glutamate, and aspartate.

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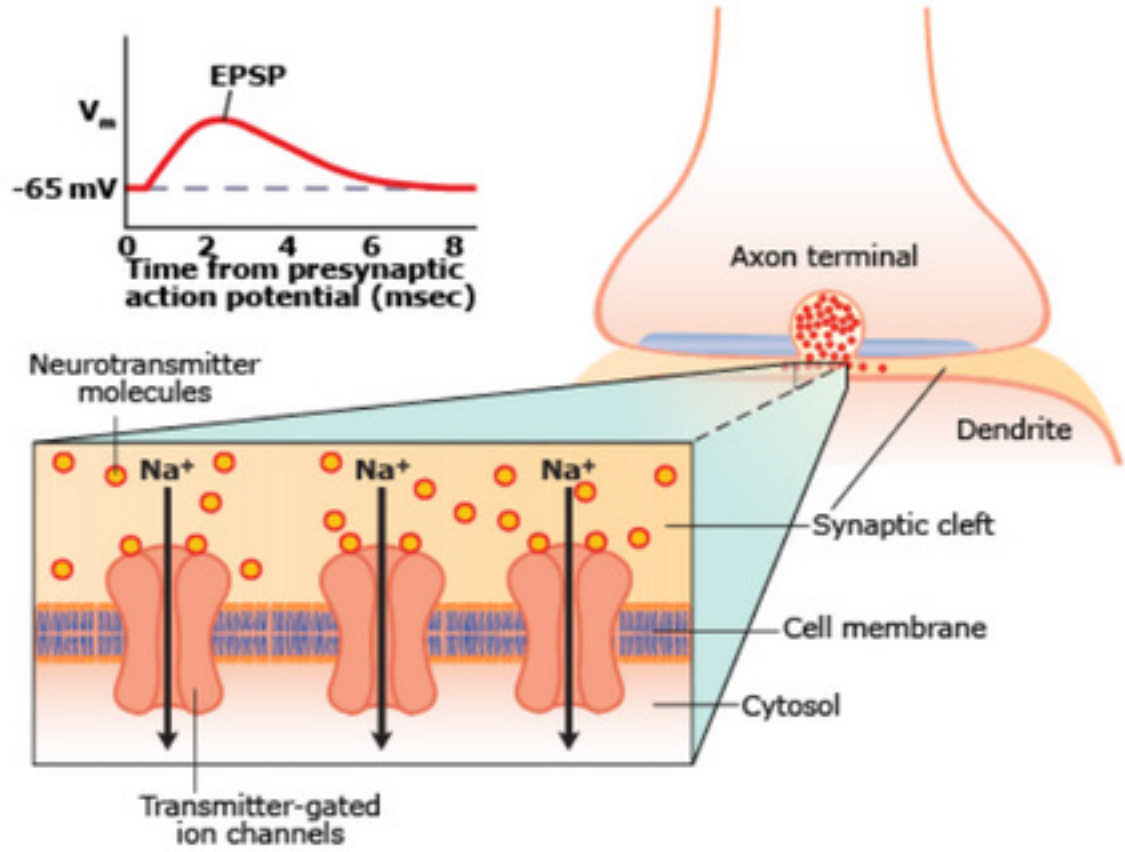
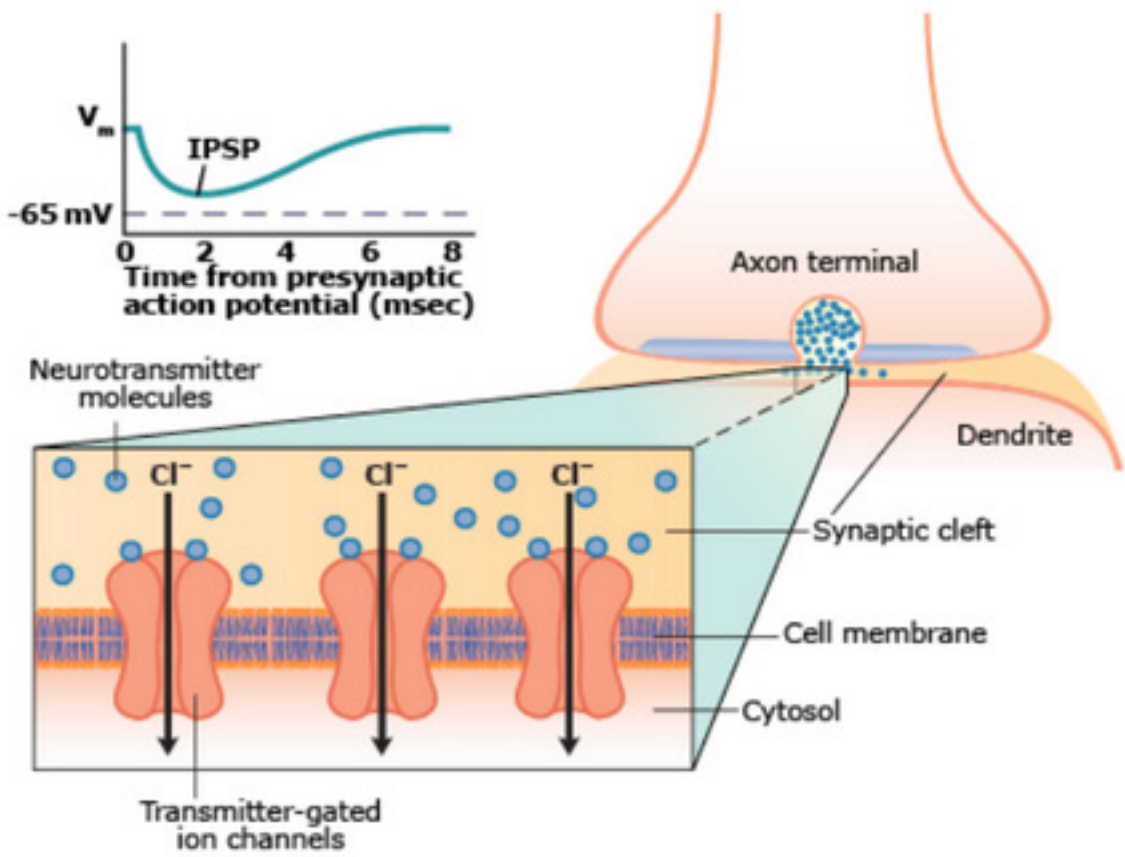


▲ **Figure 5–3.1** Characteristics of an Excitatory Postsynaptic Potential

3.2 Inhibitory Postsynaptic Potentials (IPSP)

- Transmitters in most cases hyperpolarize.
- Increased conductance of the postsynaptic membrane to Cl^- (influx) or possibly K^+ (efflux).
- Transmitters include GABA, glycine.



▲ **Figure 5–3.2** Characteristics of an Inhibitory Postsynaptic Potential

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4 Transmitters

4.1 Acetylcholine

- Excitatory transmitter in the central and peripheral nervous system.
- Action terminated by enzymatic destruction (acetylcholinesterase).
- Reuptake and recycling of choline by presynaptic membrane.

4.2 Glutamate

- The main excitatory transmitter in the central nervous system.
- Precursor to GABA.
- Action terminated by reuptake by the presynaptic membrane.

4.3 GABA and Glycine

- The two major inhibitory transmitters of the central nervous system.
- GABA predominates in the brain.
- Glycine predominates in the spinal cord.
- Utilize Cl^- channels to initiate IPSP.
- Action terminated by reuptake by the presynaptic membrane.

4.4 Biogenic Amines

- Include dopamine, norepinephrine, epinephrine, histamine, and serotonin.
- As with most transmitters, reuptake is the main mechanism of termination of synaptic action.
- Act as transmitters in the central and peripheral nervous system.

4.5 Peptides

- Unlike other transmitters that are synthesized at the nerve terminal, peptides synthesized in the cell body of the neuron.
- Action terminated by diffusion away from the synaptic region.

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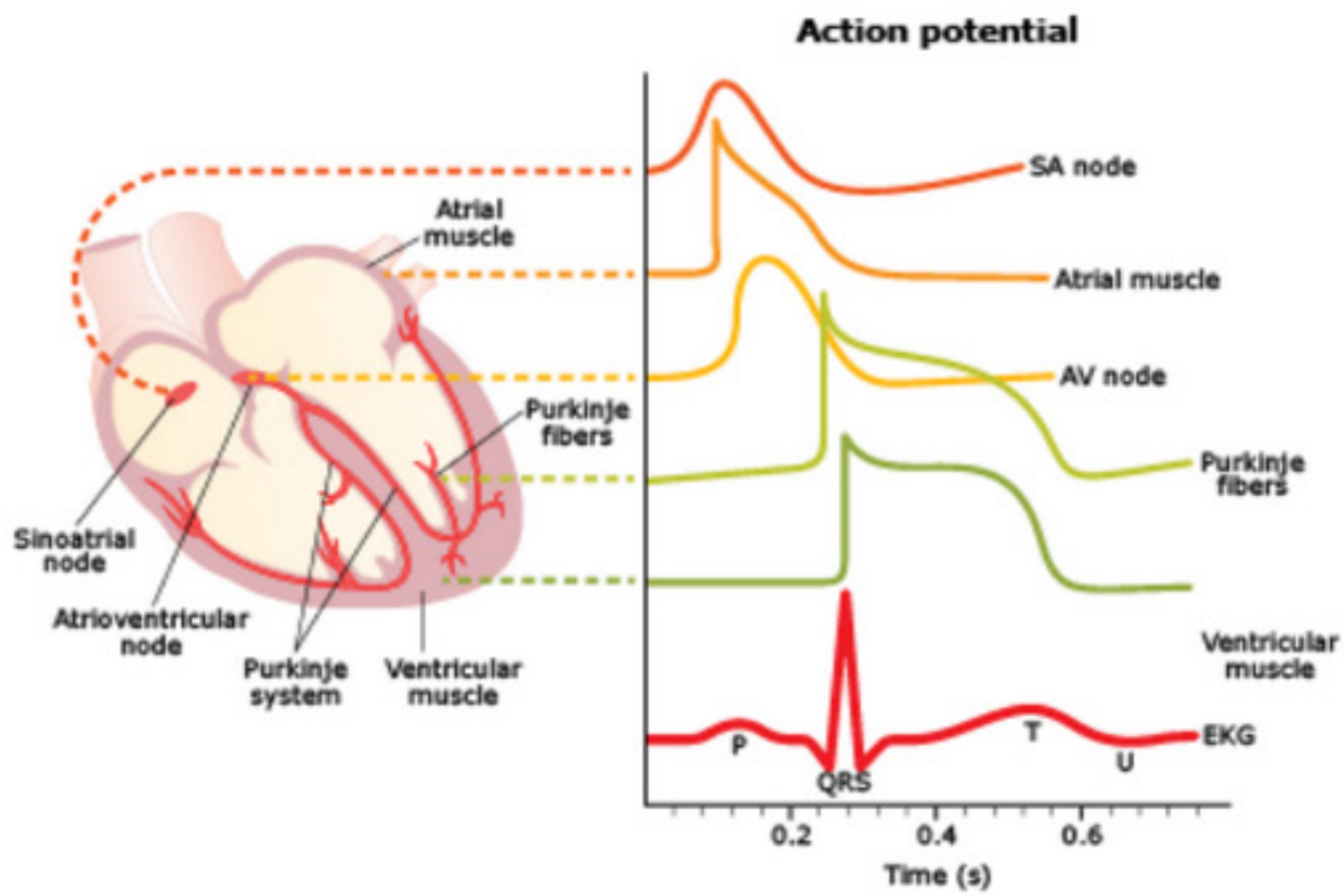
1 Introduction

There are five action potentials of the myocardium. The following figure shows the basic characteristics and the sequence in which action potentials are generated during the cardiac cycle.

SA node → atrial muscle → AV node → Purkinje fiber → contracting ventricular muscle.



▲ **Figure 6–1.0** The Five Ventricular Action Potentials

The fibers are classified in two ways:

1. Functional Differences

- **Force-Generating Cells:** Atrial fibers, ventricular muscle fibers. These fibers have a stable resting membrane potential and a long plateau phase of the action potential. The plateau is longer in the ventricular than in the atrial muscle.
- **Specialized Fibers:** SA node, AV node, Purkinje fiber. These fibers function in ways other than generating an active force during systole. Their common feature is an unstable resting membrane potential that permits them to act as pacemaker tissue.

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2. Electrical Differences

- **Fast-Responding Fibers:** Atrial fibers, ventricular muscle fibers, Purkinje fibers. All utilize fast sodium channels for the depolarization phase of the action potential (functioning fast channels = fast fiber). In addition, the resting membrane potential is more negative. As a result, depolarization has a greater magnitude and there is a greater rate of depolarization. These are the two most important features that create a high-velocity action potential. The fastest conducting fiber is a Purkinje fiber.
- **Slow-Responding Fibers:** SA nodal and AV nodal fibers. These fibers lack functioning fast channels. The depolarization phase of the action potential is generated by the slow voltage-gate Ca^{++} channel. In addition, the resting membrane potential is more positive. A smaller action potential and a slower rate of depolarization create a slower velocity for the action potential. An action potential in a slow fiber is more susceptible to blockage.

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2 The Ventricular Action Potential

2.1 Ion Channels

2.1.1 Voltage-Gated Sodium Channels

- Same characteristics as the fast channels in neurons.
- Closed state at rest, depolarization quickly activates (opens) then they quickly inactivate.
- High gNa (g = conductance) only during the depolarization phase.
- Repolarization returns them to the closed state as described for the neuron.
- The long plateau phase delays the reopening of the inactivation gate.
- Long absolute refractory period.

2.1.2 Voltage-Gated Calcium Channels

- Activate and inactivate more slowly and at a more positive membrane potential than fast channels (slow voltage-gated channels).
- Open during the plateau phase and allow influx of Ca^{++}.
- The Ca^{++} not only participates in contraction, but releases Ca^{++} from the sarcoplasmic reticulum.
- Two types: *L-type* (long-lasting) once open, remains open for a long duration. *T-type* (transient) is less abundant in heart muscle.
- Sympathetics (NE) and β-agonists (isoproterenol) ↑ gCa.
- Parasympathetics (ACH) and β-antagonists (propranolol) ↓ gCa.
- Allow some Na+ influx during the plateau.
- Can substitute for the fast channel to create depolarization, but it is slower.

2.1.3 Inward Rectifying Potassium Channel (i_{K1})

- A high-density, voltage-gated channel that is open under resting conditions (↑ gK).
- Functions as the K^+ "leak" channels.
- High gK at rest results in Em (−90 mV) being very close to E_K (−94 mV).
- Almost all close near the end of depolarization, remain closed during the plateau and reopen during repolarization.
- Their closing is responsible for the low gK during the plateau phase. Plateau phase will not develop unless these channels close.

2.1.4 Transient Outward Potassium Channel (i_{to})

- Opens transiently at the beginning of the plateau phase.
- Creates the *phase 1* of epicardial, midmyocardial fibers of the ventricular myocardium and Purkinje fibers.
- Most are closed during the main part of the plateau.

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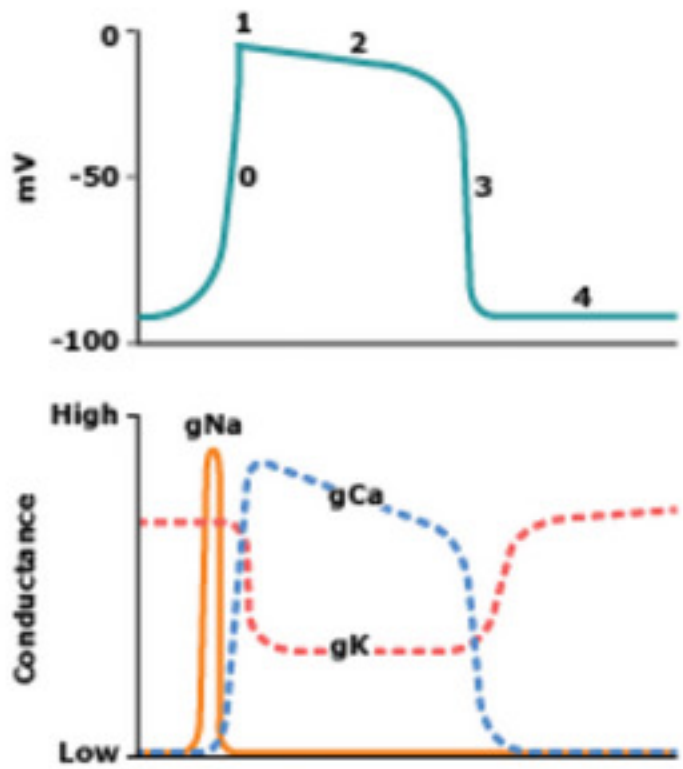
2.1.5 Delayed Rectifying Potassium Channel (i_K)

- Closed under resting conditions.
- Slowly open in response to depolarization.
- Small percentage open during the plateau to support a potassium efflux.
- Open more rapidly near the end of the plateau to initiate repolarization.
- Rate of opening determines the length of the plateau (faster opening in atrium).
- Can be considered similar but not identical to the voltage-gated K^+ channels of neurons.

2.2 Phases of the Ventricular Action Potential



▲ **Figure 6–2.2** Conductance Changes During the Ventricular Action Potential

2.2.1 Phase 0

- ↑ gNa due rapid activation of the fast channels.
- Na^+ influx creates the depolarization phase.
- Depolarization decreases inward force on Na^+ but increases to outward force on K^+.
- Channels have inactivated before entering the plateau phase.
- Class I antiarrhythmics (procainamide) ↓ gNa, ↓ rate of depolarization.
- Complete blockage of fast channels creates a slow fiber.

2.2.2 Phase 1

- Transient outward K^+ current (i_{to}).
- Absent in endocardial fibers.

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2.2.3 Phase 2

- ↑ gCa due to activation of the L-type channel and an influx of Ca^{++}.
- The Ca^{++} participates in contraction and triggers the release of Ca^{++} from the sarcoplasmic reticulum. If no influx, no Ca^{++} for contraction.
- Low gK during the plateau compared to phase 4.
- If no big ↓ gK, plateau does not develop.
- Most of the i_{K1} and i_{to} channels have closed, and i_K channels are just beginning to open.
- The inward Ca^{++} is balanced by the outward K^+, creating a plateau.
- Ca^{++} channel antagonists (diltiazem, a Class IV antiarrythmic) shorten, and K^+ channel antagonists (amiodarone, a Class III antiarrythmic) lengthen plateau phase.
- Some Na^+ influx continues during the plateau.
- Plateau duration is a major factor in determining the length of the absolute refractory period.

2.2.4 Phase 3

- Initiated by a rapid increase in gK due to opening of the i_K channels.
- K^+ efflux greater than Ca^{++} influx.
- ↓ gCa toward zero eliminates Ca^{++} influx.
- Once initiated, reopening of the i_{K1} channels speeds and rapidly completes the process of repolarization.

2.2.5 Phase 4

- Low gNa and gCa, but high gK.
- Na/K-ATPase pump reestablishes Na-K gradients, and mainly secondary active transport reestablishes Ca^{++} gradient (3 Na^+ per 1 Ca^{++}).

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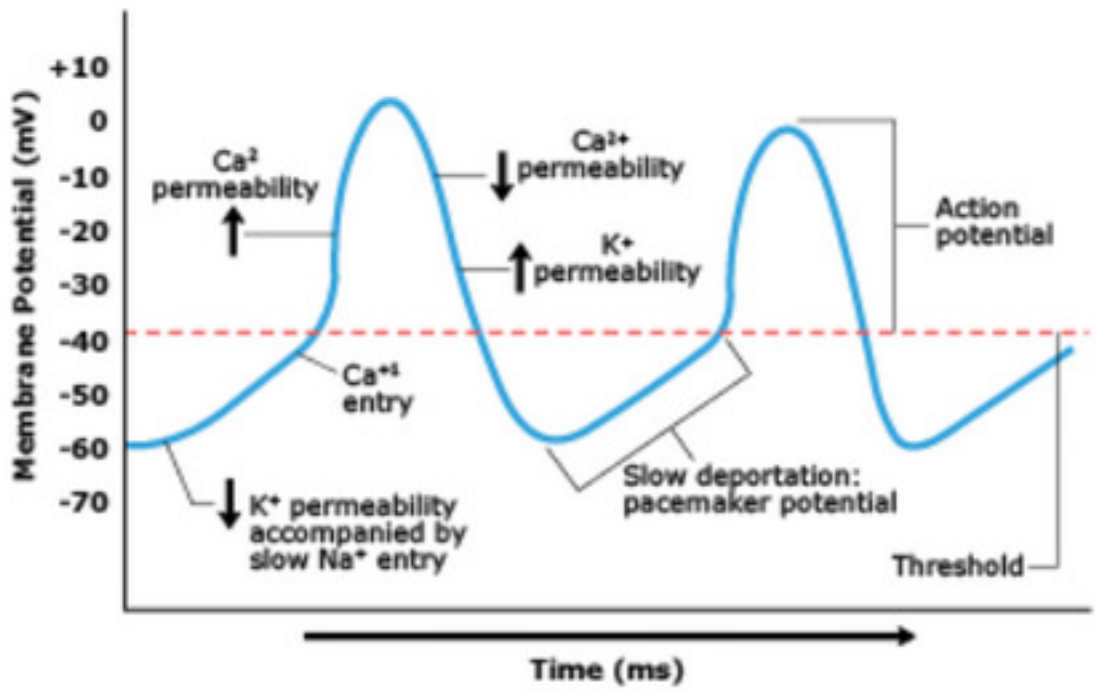
3 Slow Fiber Action Potentials

Major differences with a fast fiber include a more positive E_m in phase 4 and no functioning fast channels. The slower rate of depolarization and the overall smaller magnitude of the action potential not only slow conduction velocity, but increase the probability of blockage. All specialized fibers have a gradual depolarization toward threshold in phase 4 (pacemaker or prepotential). Thus, they do not need an external stimulus to generate action potentials. The following figure is an action potential from an SA nodal fiber.



▲ **Figure 6–3.0** Characteristics of an SA Nodal Action Potential

3.1 Phase 4

- Decreasing gK reducing K^+ efflux.
- Open voltage-gated Na^+ channels (*funny channels*) and Na^+ influx (*funny current*).
- Increase in gCa near the end of phase 4.
- All three of the preceding contribute to the pacemaker potential.

3.2 Phase 0

- Activation of L-type Ca^{++} channels and a Ca^{++} influx.
- Decreased slope and magnitude of the action potential compared to a fast fiber.
- Ca^{++} channel antagonists reduce the slope and magnitude of phase 0.
- Fast channel blockers have no effect.
- No phase 1 and no significant phase 2.

3.3 Phase 3

- ↑ gK due to activation of channels similar to i_K.
- Repolarization due to K^+ efflux.

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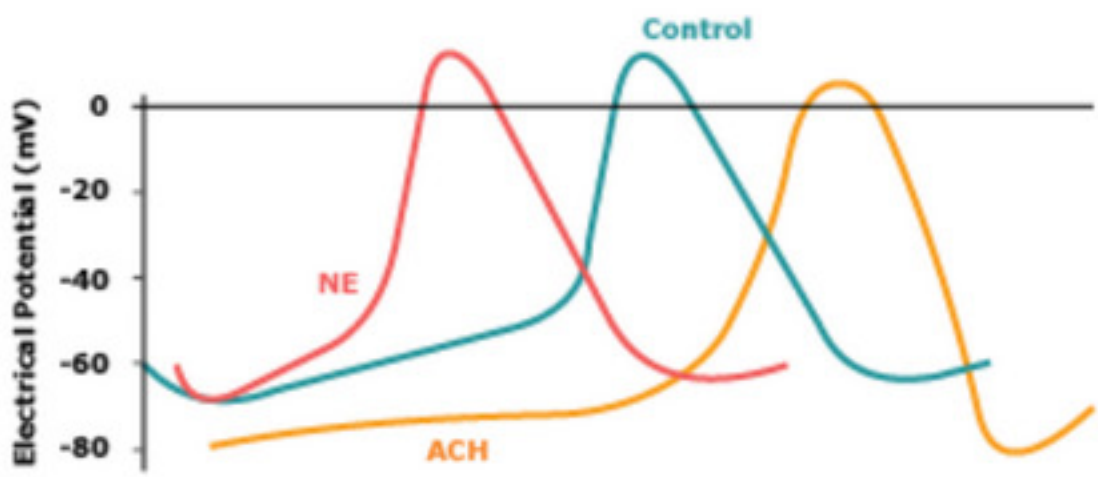
4 Effect of Autonomic Fibers

4.1 Sympathetics

- Increase in K, Na, and Ca currents during phase 4.
- Increased slope of the prepotential.
- Increased firing rate.

4.2 Parasympathetics

- Decrease in Na and Ca currents and increased gK.
- Hyperpolarization and decreased slope of the prepotential.
- Decreased firing rate.



▲ **Figure 6–4.2** Autonomic Effects on the SA Node Action Potential

5 Overdrive Suppression

Automaticity: SA node = 100–110/min

AV node = 50–60/min

Purkinje fiber = 30–35/min

If a pacemaker tissue receives high-frequency electrical pulses, its own intrinsic rate is temporarily suppressed (e.g., the AV node receives impulses from the SA node greater than its own intrinsic rate). Because the AV node's intrinsic rate is temporarily suppressed, if SA node input were to suddenly cease, there would be a pause before the AV node recovers.

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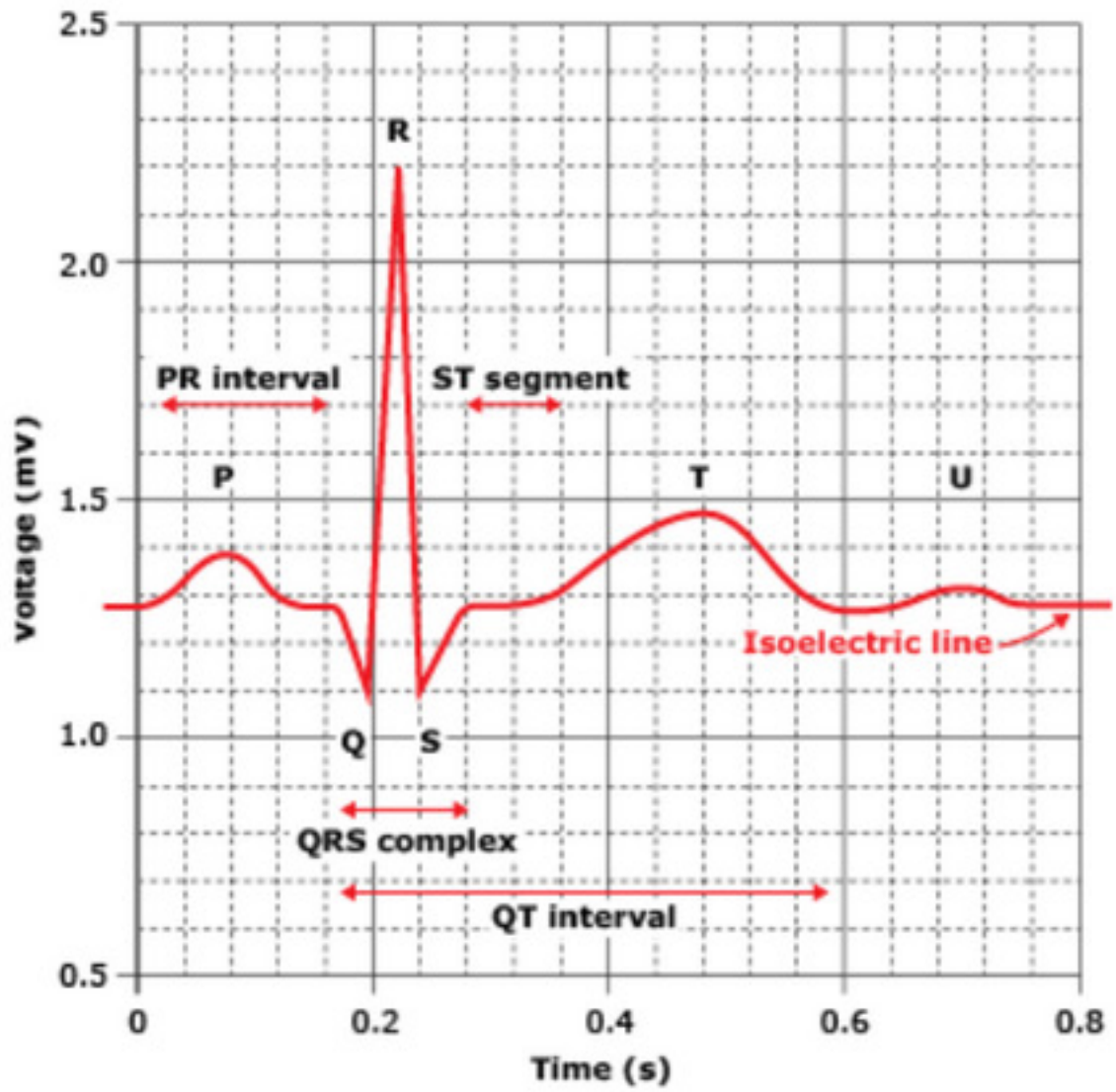
6 Electrocardiography

6.1 Electrocardiogram



▲ **Figure 6–6.1** Components of an EKG

6.1.1 P Wave—Atrial Depolarization

6.1.2 QRS—Depolarization of Left and Right Ventricle

- Maximal normal duration 0.12 seconds.
- A prolonged QRS complex indicates a conduction problem in the ventricles.
- Q wave: First downward deflection prior to an R wave (may or may not be present).
- R wave: First upward deflection whether preceded by a Q wave or not.
- S wave: Downward deflection following an R wave.

6.1.3 T wave—Repolarization of Left and Right Ventricle

6.1.4 PR Interval—Beginning of the P Wave to the Beginning of the QRS Complex

- Depolarization of RA, LA, passage through AV node and depolarization of Purkinje system.
- 0.12–0.20 seconds.

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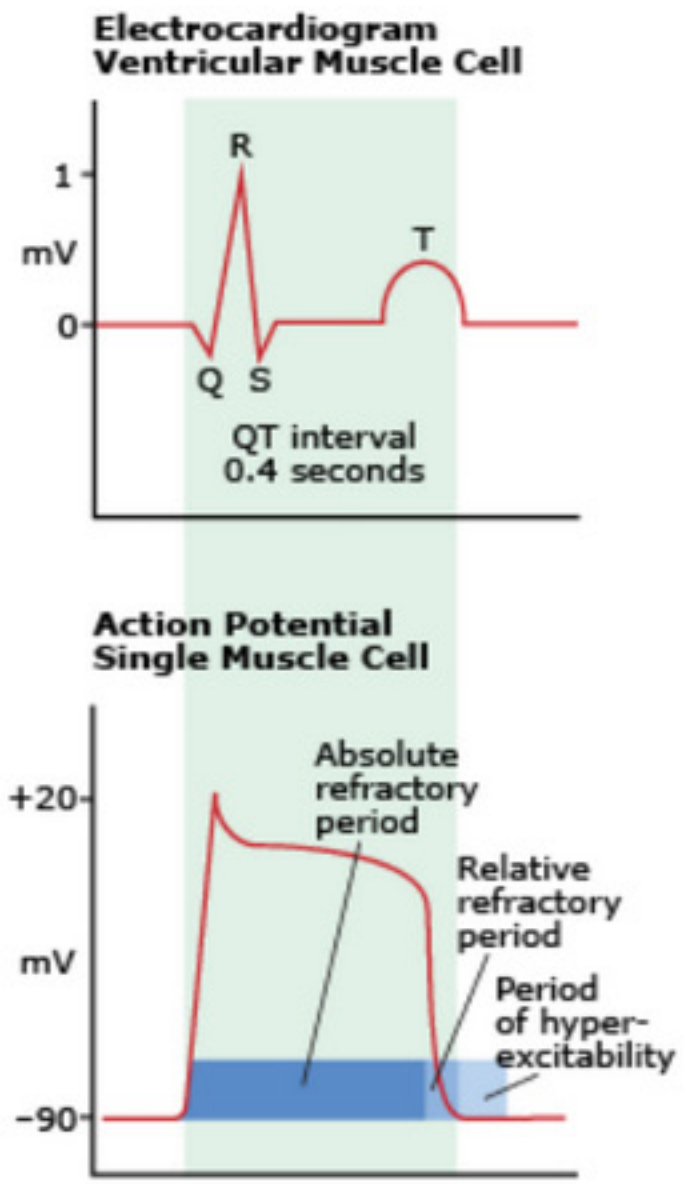
6.1.5 QT Interval—Beginning of the QRS to the End of the T Wave

- Duration of the ventricular action potential.
- Prolonged: males > 0.44 seconds; females > 0.435 seconds.

6.1.6 ST Segment—Isoelectric Line Between the QRS Complex and T Wave

- Entire ventricular myocardium depolarized.
- Depolarization proceeds from endocardium to epicardium.
- Repolarization proceeds from epicardium to endocardium.
- Corresponds with the plateau phase of the ventricular action potential.
- ST segment depression in subendocardial ischemia.
- ST segment elevation in transmural ischemia.

6.2 Correlation of EKG to Ventricular Action Potential



▲ **Figure 6–6.2** Correlation of the EKG With the Ventricular Action Potential

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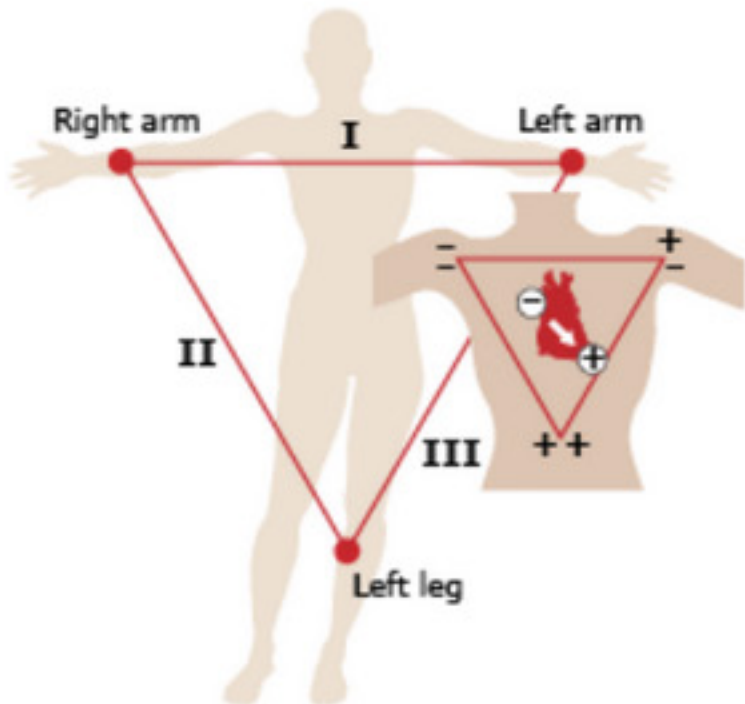
6.3 Standard EKG Leads:

Composed of 12 leads:

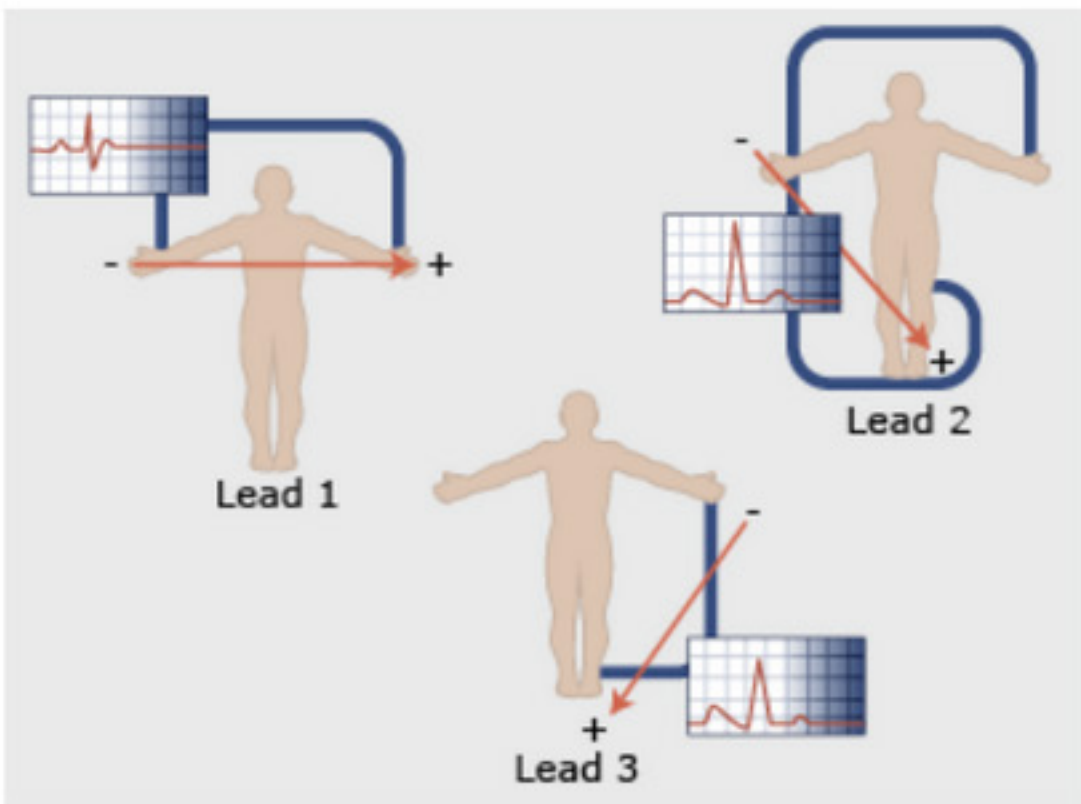
- Six frontal leads (bipolar leads, unipolar leads)
- Six precordial leads

Einthoven's Triangle



▲ **Figure 6–6.3A** Einthoven's Triangle

6.3.1 Bipolar Leads



▲ **Figure 6–6.3B** Bipolar Limb Leads

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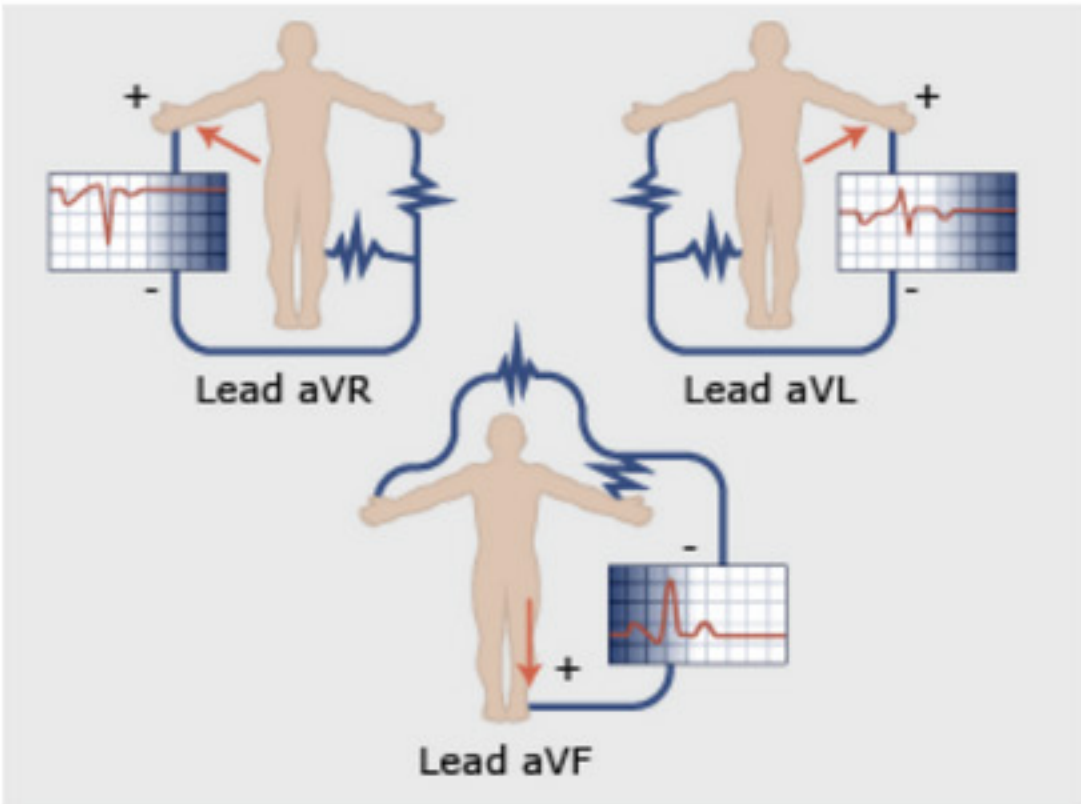
6.3.2 Unipolar Leads

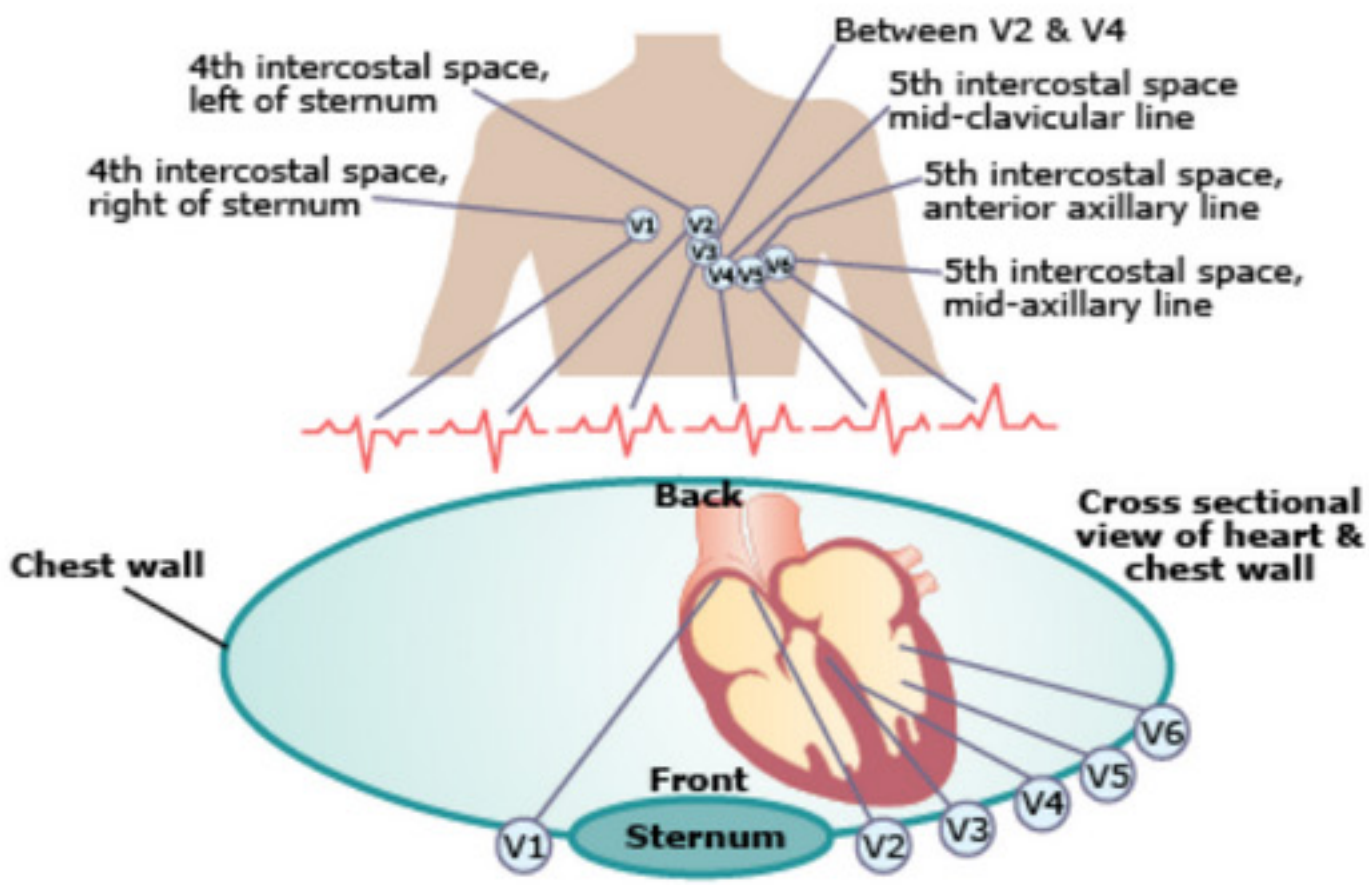
Potential difference between an anatomic point and the zero potential point (chest center).



▲ **Figure 6–6.3C** Unipolar (Augmented) Limb Leads

6.3.3 Precordial Leads

Six Unipolar Leads (V1–V6).



▲ **Figure 6–6.3D** Precordial Chest Leads

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6.4 Abnormal Conduction: Heart Block

6.4.1 First-Degree AV Block

- Prolonged PR interval (> 0.2 seconds).
- Delay typically in the AV node itself.
- Usually benign when seen without further block.
- May be associated with increased vagal tone, drugs, and electrolyte disturbances.

▲ **Figure 6–6.4A** First-Degree Heart Block EKG

6.4.2 Second-Degree AV Block

- Some of the atrial impulses not transmitted through the AV node.
- Wenckebach (Mobitz Type I).
- Mobitz Type II.

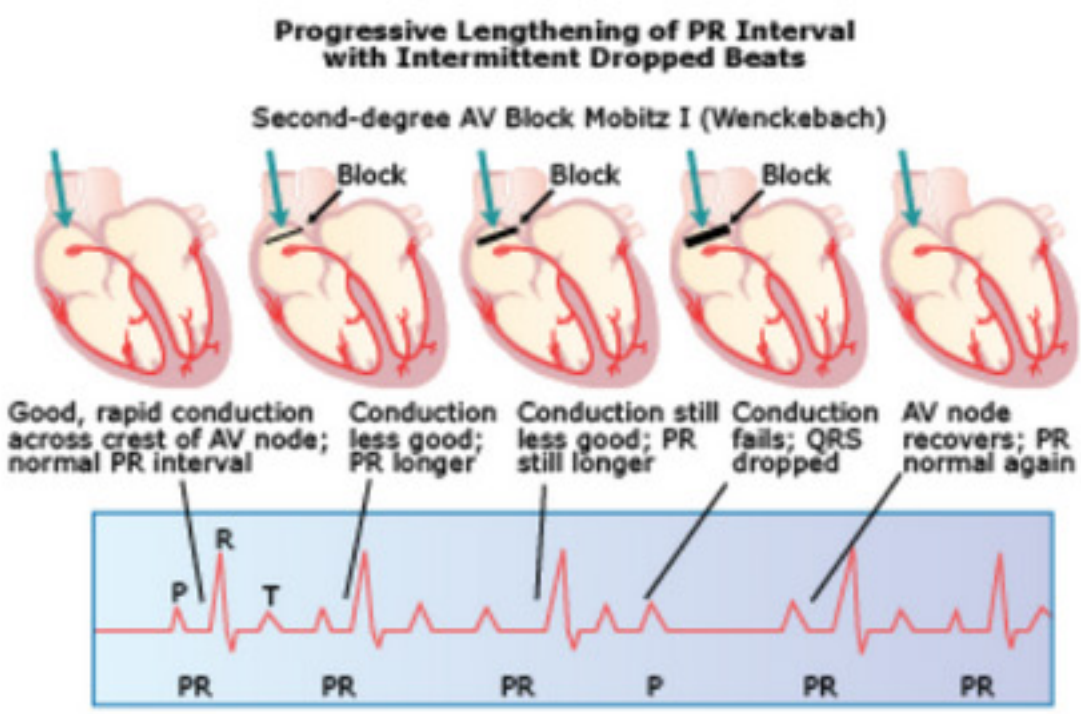
▲ **Figure 6–6.4B** Second-Degree Heart Block EKG

6.4.3 Third-Degree AV Block

- Complete AV block.
- Atrial and ventricular rhythms independent of each other.
- No correlation of P waves and QRS complexes.
- Frequency of P waves greater than QRS complexes.

▲ **Figure 6–6.4C** Third-Degree Heart Block EKG

6.4.4 Second-Degree AV Block: Mobitz 1



▲ **Figure 6–6.4D** Characteristics of Second-Degree Heart Block: Mobitz I (Wenckebach)

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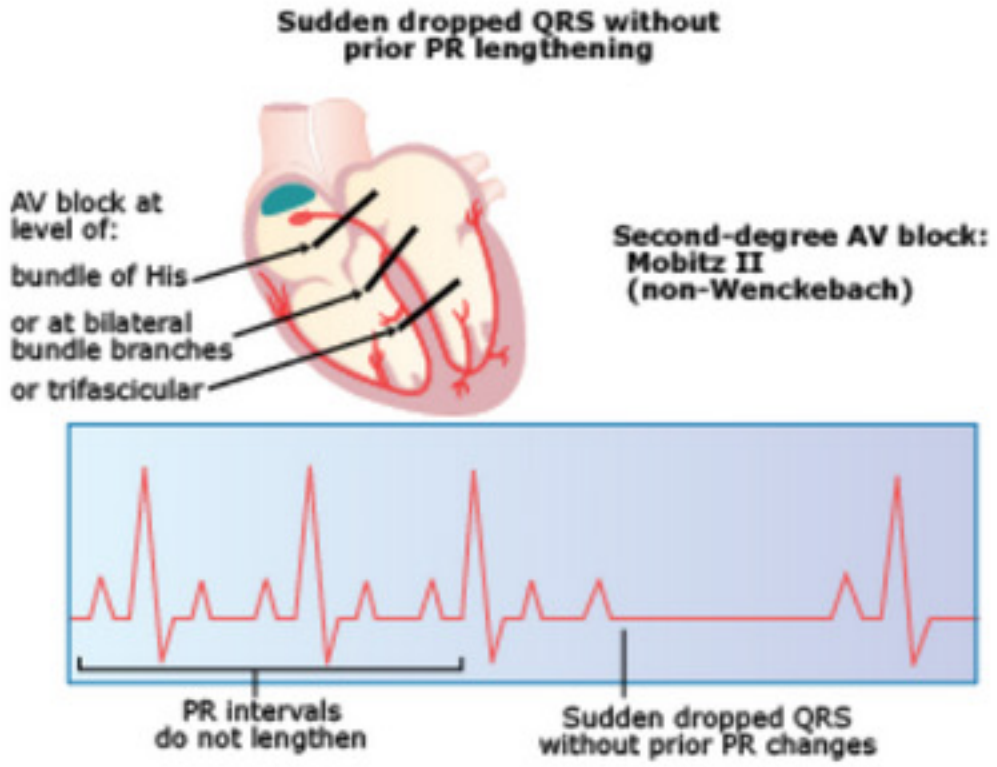
6.4.5 Second-Degree AV Block: Mobitz II

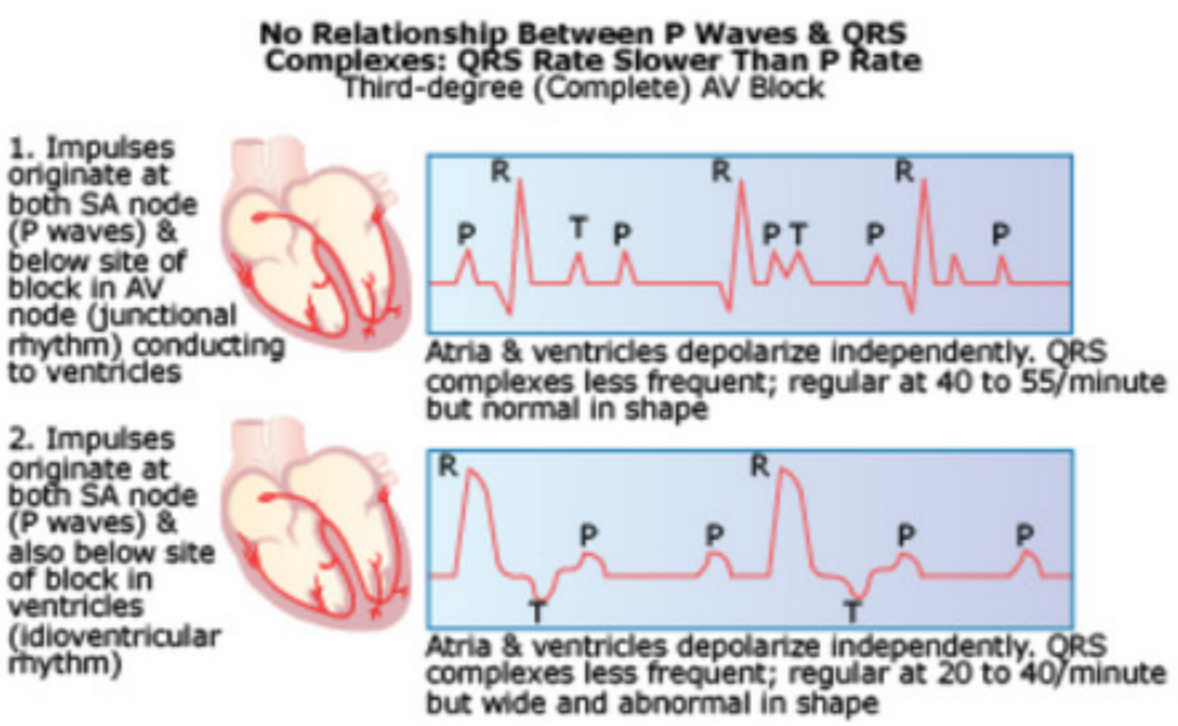
Dropped QRS, unchanged PR interval.



▲ **Figure 6–6.4E** Characteristics of Second-Degree Heart Block: Mobitz II

6.4.6 Third-Degree AV Block

- Complete heart block.
- Impulse unable to pass AV node.
- Atrial and ventricular rhythms independent of each other.



▲ **Figure 6–6.4F** Characteristics of Third-Degree Heart Block

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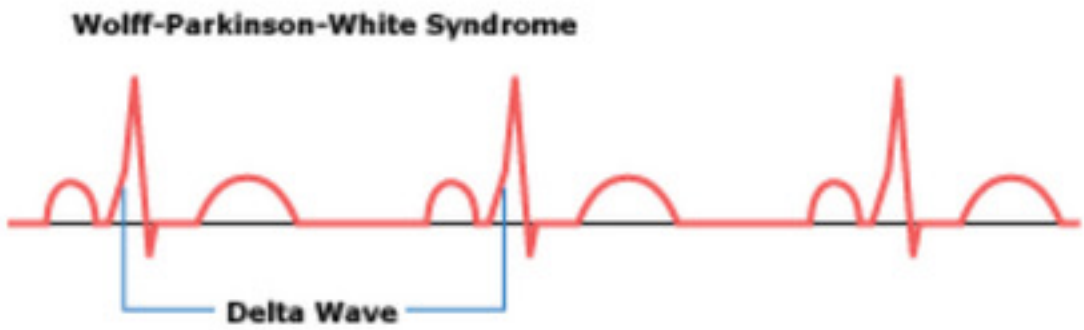
6.5 Conduction Disturbances:

Wolff-Parkinson-White syndrome:

- Abnormal accessory path between atria and ventricles.
- No delay in impulse conduction.
- EKG: Short PR interval, wide QRS, slurred initial upstroke of R wave (delta wave).



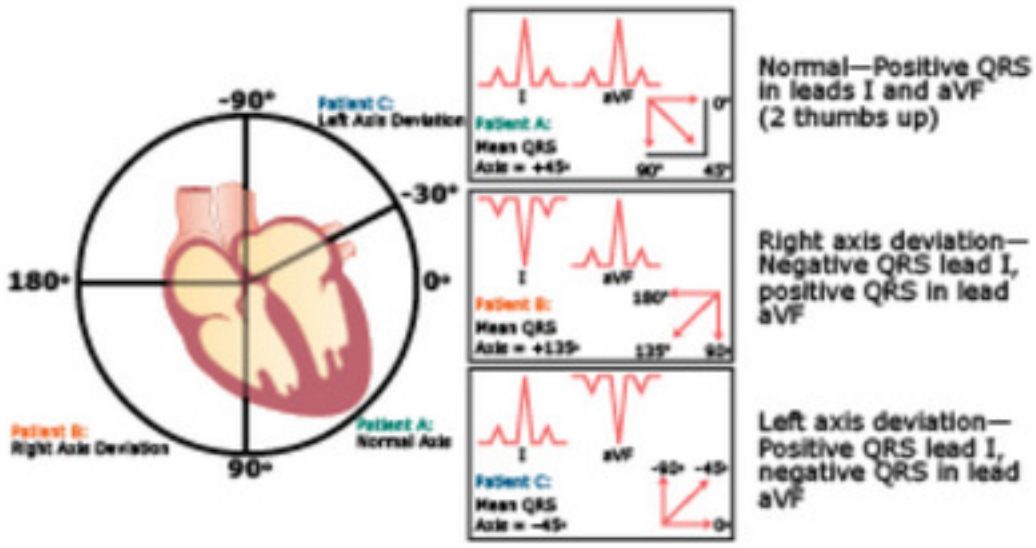
▲ **Figure 6–6.5** Wolff-Parkinson-White Syndrome EKG

6.6 Mean Electrical Axis

- Indicates the net direction of the electrical current during depolarization.
- Normally about +60 degrees, normal range 0–90 degrees, QRS in leads I, II, III usually all upright.
- > +60 degrees in tall, thin individuals, < +60 degrees in short, obese individuals.
- Left axis deviation: left ventricular hypertrophy, conduction problems in left ventricle (except posterior bundle).
- Right axis deviation: right ventricular hypertrophy, conduction problems in right ventricle and posterior bundle left ventricle.
- Generalization: Axis moves toward hypertrophied tissue and away from infarcted tissue.

6.6.1 Axis Deviation

- Normal—Positive QRS in leads I and aVF.
- Left axis deviation—Positive QRS lead I, negative QRS in lead aVF.
- Right axis deviation—Negative QRS lead I, positive QRS in lead aVF.



▲ **Figure 6–6.6** Left Axis and Right Axis Deviation EKG

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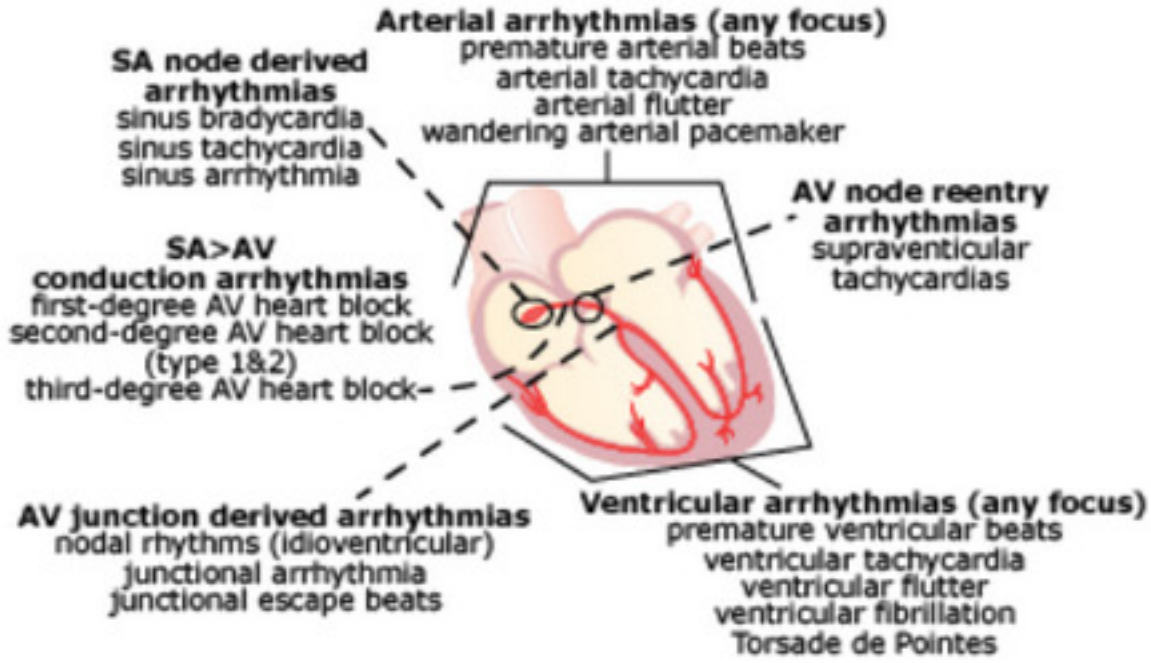
6.7 Abnormal Rhythms

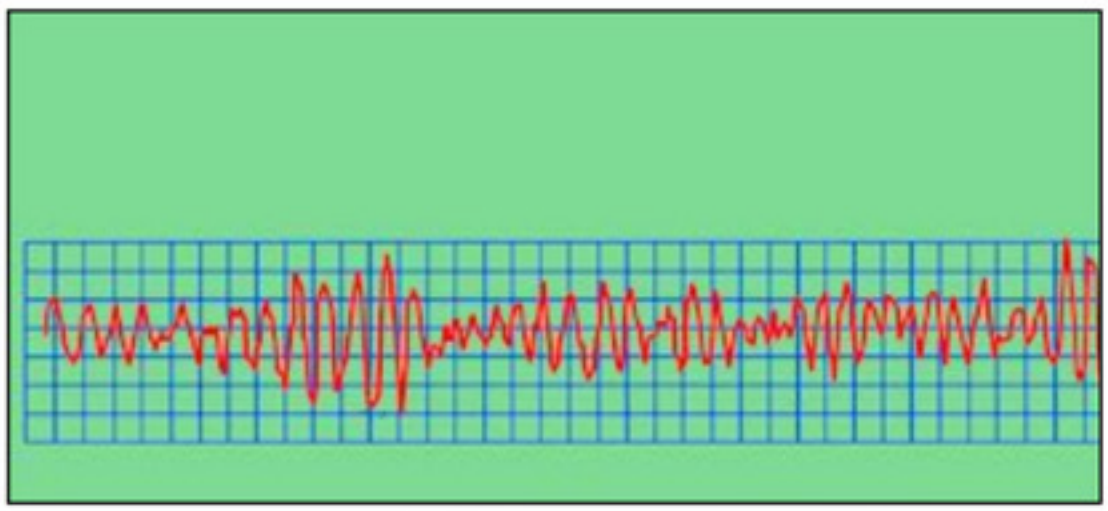


▲ **Figure 6–6.7** Summary of Abnormal Rhythms

6.8 Torsade de Pointes

- Polymorphic, gradual change in QRS amplitude.
- "Swings around a point".
- Associated with prolonged QT.
- Causes:

  Bradycardia, electrolyte disturbances (hypokalemia, hypomagnesemia).



▲ **Figure 6–6.8** Torsade de Pointes EKG

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Unit 3

Muscle Physiology

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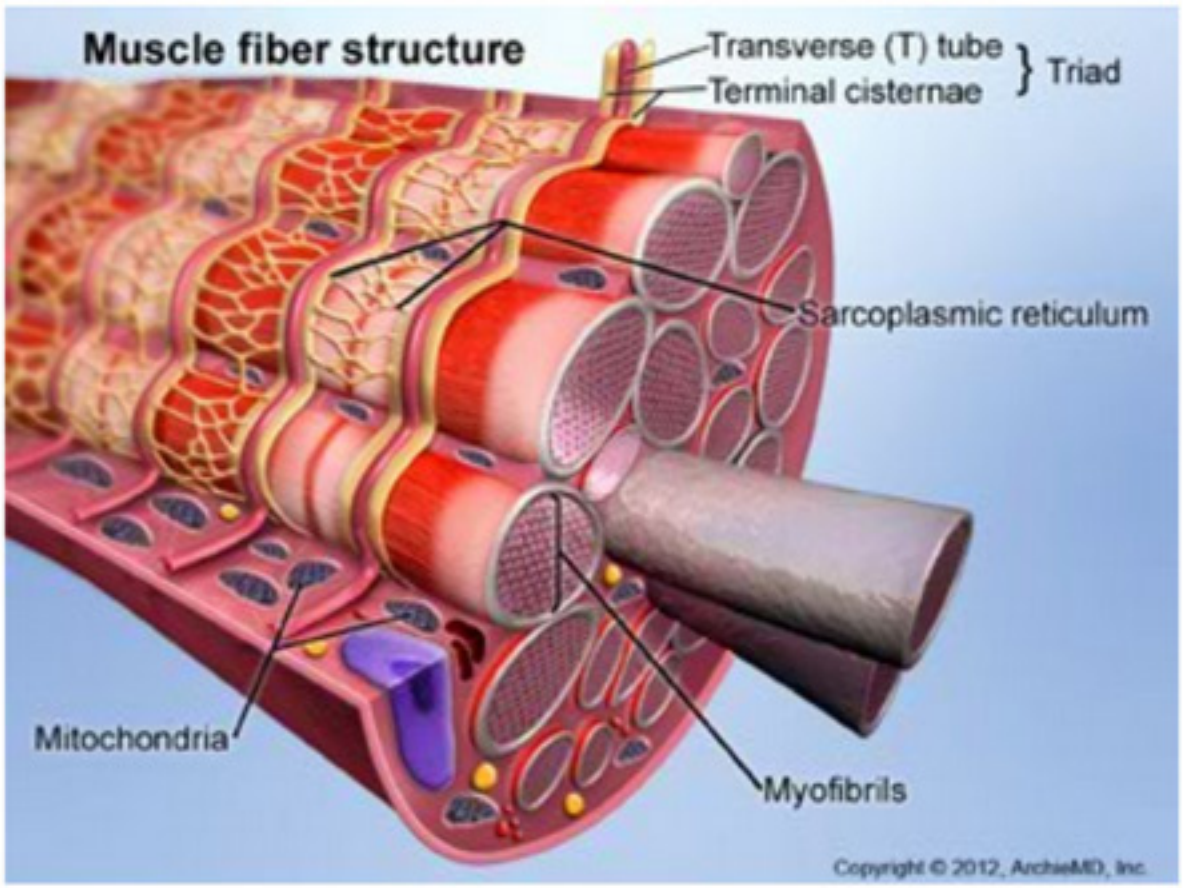
1 Organization of a Muscle Cell

1.1 Skeletal Muscle



▲ **Figure 7–1.1** Muscle Fiber Structure

- Each muscle is composed of individual muscle cells called *fibers* that usually run the entire length of the muscle.
- Each fiber is innervated and the fibers are organized into motor units.
- Type I: Slow red muscle: Small fibers, small motor units, lower ATPase, endurance muscle, aerobic metabolism, extensive capillaries, high myoglobin, as in the soleus muscle.
- Type II: Fast white muscle: Large fibers, large motor units, high ATPase, high strength but short term, anaerobic metabolism, extensive sarcoplasmic reticulum, low myoglobin, as in sprinter's leg muscles, ocular muscles.
- Each muscle fiber contains hundreds of fibrils arranged in parallel.
- Each fibril composed of sarcomeres connected in series (end-to-end).
- Striated muscle: Actin and myosin organized into sarcomeres.

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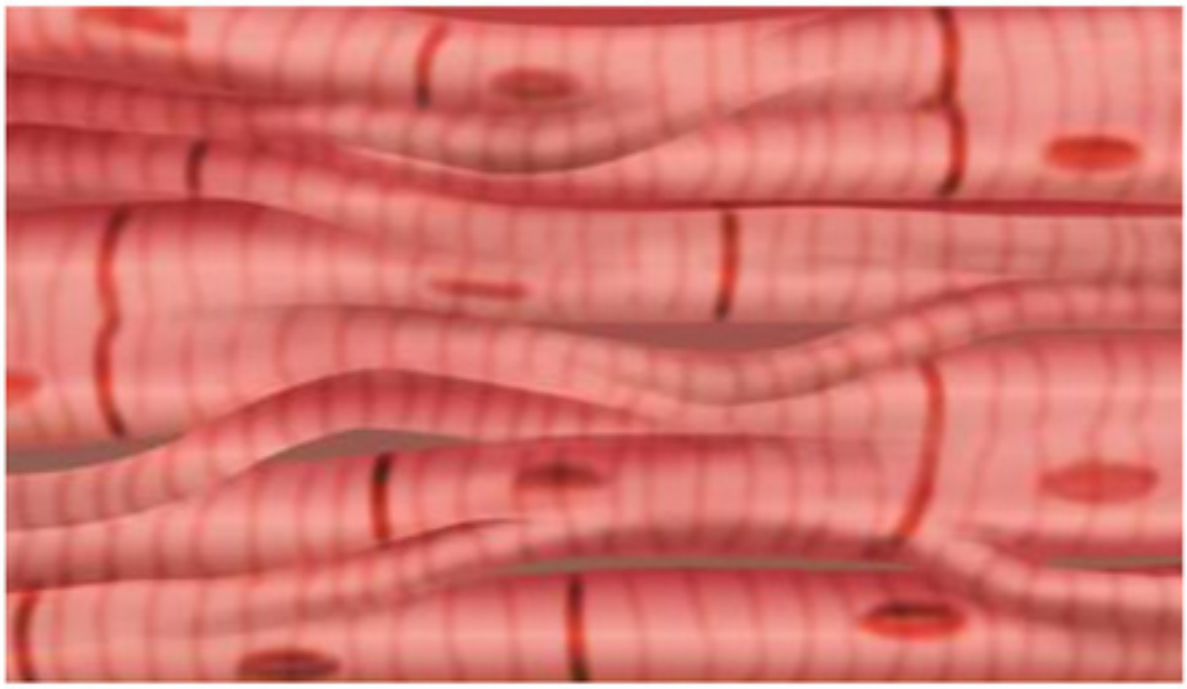
1.2 Cardiac Muscle



▲ **Figure 7–1.2** Interconnecting Nature of Cardiac Muscle

- Small muscle cells: Aerobic metabolism, high myoglobin, extensive capillaries, intermediate ATPase.
- Connected via intercalated discs that contain gap junctions.
- Intercalated discs form a mechanical and electrical syncytium.
- Myocytes contain myofibrils consisting of sarcomeres connected in series.

1.3 Smooth Muscle

- Very small muscle cells.
- Adherens provide mechanical connections between cells.
- Gap junctions provide electrical connections between cells.
- Mechanical-electrical syncytium.
- Multi-unit smooth muscle: Each fiber innervated and, because fibers are insulated, they can contract independently, as in ciliary, iris muscles of the eye.
- Unitary smooth muscle: Fiber mass contracts as a unit via gap junctions, syncytial or visceral smooth muscle, as in the bladder smooth muscle.
- Very slow muscle: Low ATPase, does not fatigue unless deprived of oxygen.
- Actin attached to dense bodies.
- Actin and myosin not organized into sarcomeres (unstriated muscle), but filaments mechanically linked from cell to cell.

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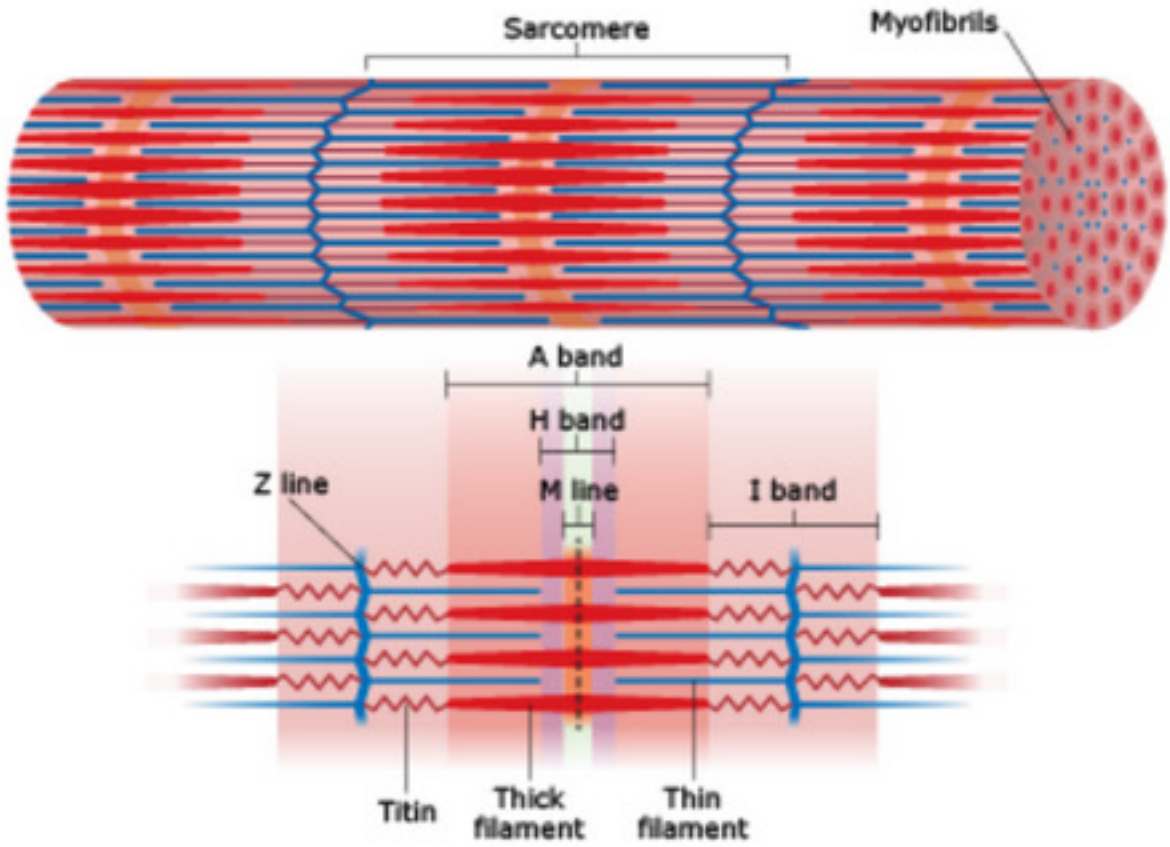
2 Organization of Actin and Myosin Filament

2.1 Sarcomere (Skeletal and Cardiac Muscle)



▲ **Figure 7–2.1** Organization Within a Sacromere

- Sarcomeres connected in series delineated by Z lines.
- Thin filaments: Composed of actin molecules (G-actin) strung together to form two-stranded helical filaments (F-actin) connected at the Z lines.
- Thick filaments: Composed of heavy and light chain myosin wound together to form a rod-like filament connected to the Z line via the very elastic protein titin.
- A band: Length of the myosin on either side of the M line, length stays constant during contraction.
- I band: Length of the thin filament on either side of the Z line with no overlap with the thick filaments; length decreases during contraction when the actin and myosin slide past one another.

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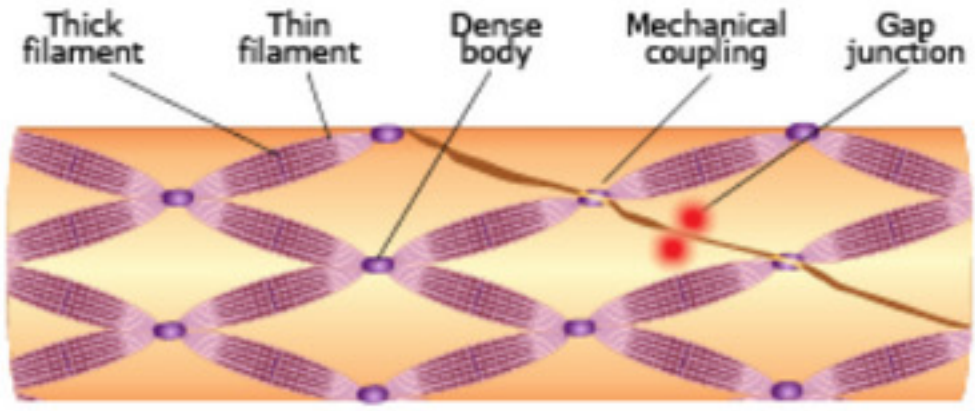
2.2 Unstriated Actin-Myosin Smooth Muscle



▲ **Figure 7–2.2** Smooth Muscle Actin-Myosin Organization

- Actin attached to dense bodies (equivalent to Z lines).
- Group of thick and thin filaments (equivalent to sarcomeres) mechanically linked cell to cell to form a series-connected contractile machinery.
- Cross-bridge heads have low ATPase and cycle slowly during contraction.
- Greater sliding of actin and myosin past each other during contraction increases force of contraction.
- Latch mechanism: Very slow cycling of cross-bridges allows maintenance of active force with minimal energy consumption.

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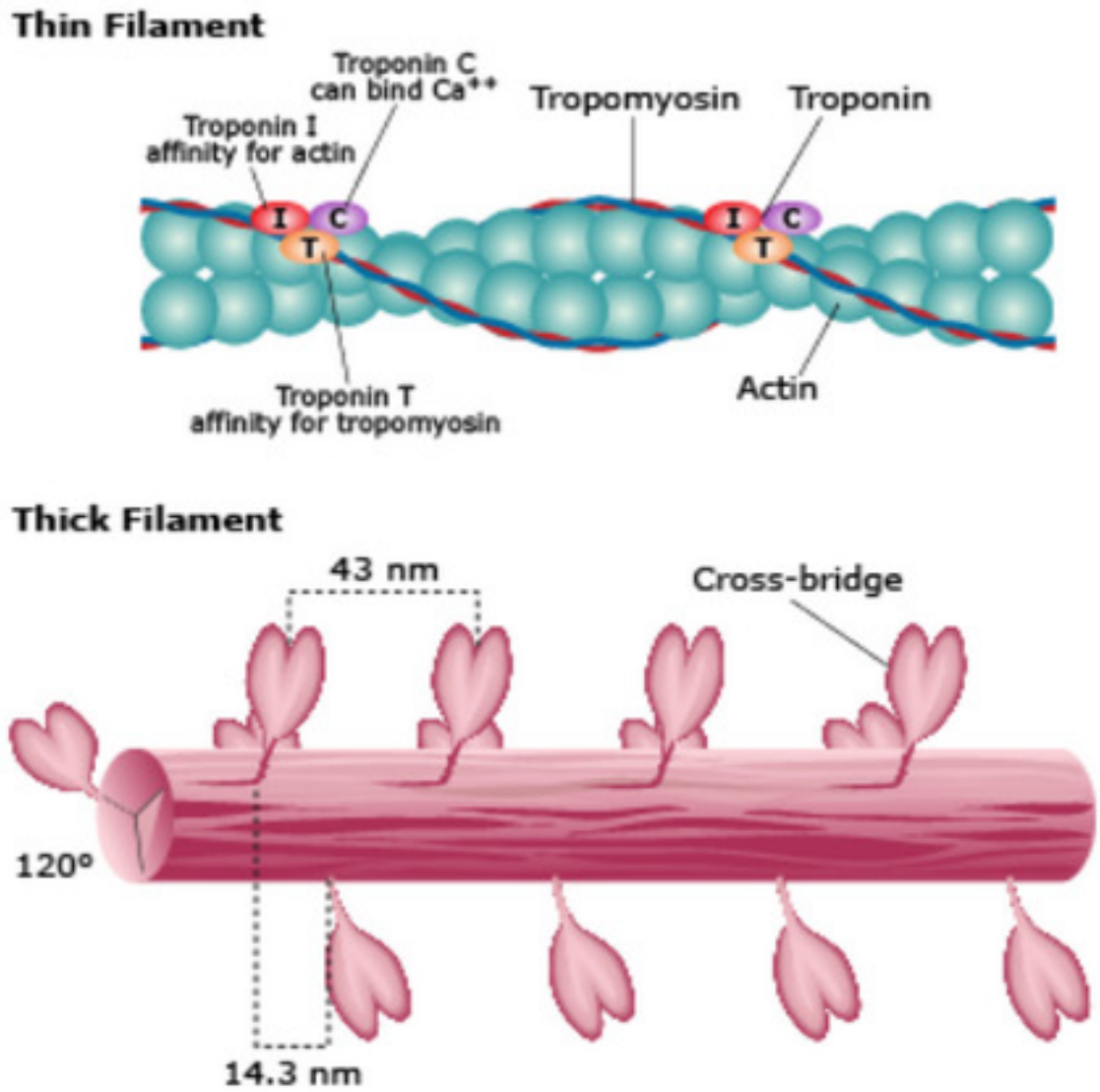
3 Organization Within Thin and Thick Filaments of Skeletal and Cardiac Muscle



▲ **Figure 7–3.0** Thin and Thick Filaments Substructure

3.1 Thin Filament Organization

- Actin: Structural protein of the thin filament, G-actin has the active attachment sites for the cross-bridges.
- Tropomyosin: A dimer that extends over about seven G-actins, physically covering the active sites in a resting muscle.
- Troponin: In contact with the tropomyosin and contains three subunits:
  - Troponin I has affinity for the actin
  - Troponin T has affinity for the tropomyosin
  - Troponin C can bind Ca^{++}
- Calcium Interactions:
  - At rest, no calcium attached to troponin, active sites unavailable.
  - Calcium attaches to troponin to initiate contraction, tropomyosin pulled deep into the groove between actin filaments to expose active sites.
  - Calcium removed from the troponin to terminate contraction, tropomyosin moves back to cover the active sites.

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3.2 Thick Filament Organization

- Heavy and light myosins form the rod-like thick filaments.
- Cross-bridges: Integral part of thick filament that consist of an arm and globular head, and characterized by the following features:
  - Two flexible, hinge-like points where the arm leaves the body of the thick filament and where the head attaches to the arm.
  - Movement of the head relative to the arm when attached to the actin provides the power stroke during contraction.
- Cross-bridge heads have ATPase activity and gain and lose affinity for the G-actin during contraction.
- ATPase breaks down ATP during contraction to supply the energy for the power stroke of the cross-bridge head.

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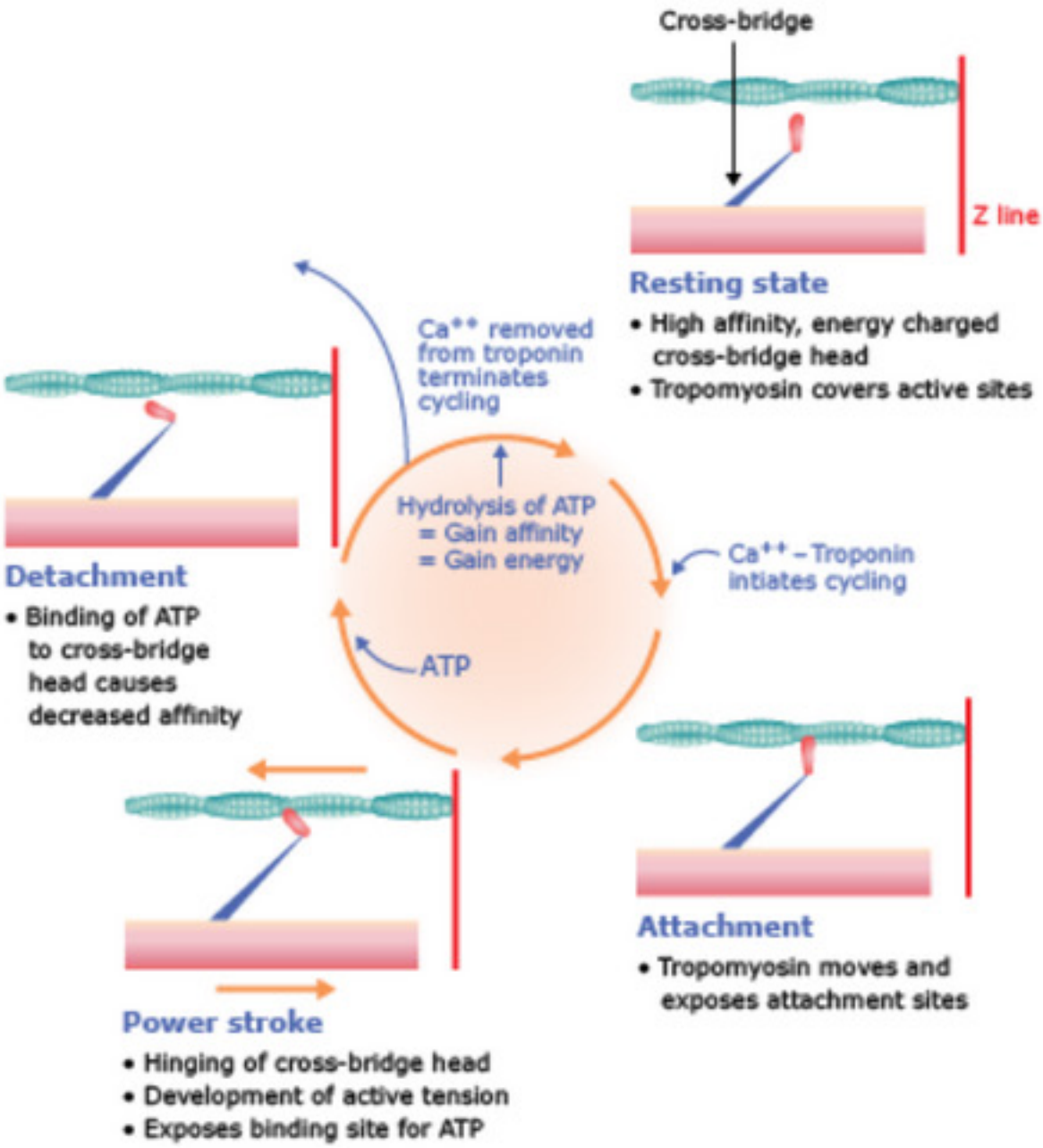
4 Cross-Bridge Cycling: The Sliding Filament Theory of Muscle Contraction

4.1 Skeletal and Cardiac Muscle



▲ **Figure 7–4.1** Cross-Bridge Cycling

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4.1.1 Important Points

- Contraction is the cycling of the cross-bridges.
- Cycling is initiated by ICF free Ca^{++} attaching to troponin, first cross-link forms.
- ATP is not required to start the cycling and contraction.
- Attachment of ATP breaks the cross-link between the actin and myosin.
- Cycling continues (contraction continues) until Ca^{++} removed from the troponin.

Note: Following death, the muscle cell becomes ATP depleted, Ca^{++} leaks from the sarcoplasmic reticulum and attaches to troponin to form a cross-link between the actin and myosin; but, no ATP means the crosslink will not break. This is the state of rigor mortis. Lysosomal enzymes eventually break the link to terminate the state of rigor mortis.

Memory Aid

Contraction is an active process requiring ATP.

Rigor mortis is a passive process requiring free ICF Ca^{++} in the absence of ATP.

4.2 Smooth Muscle

- Skeletal and cardiac muscle initiates contraction via an actin-activated process (Ca^{++} to troponin).
- Smooth muscle initiates contraction via a myosin activation process (Ca^{++} to calmodulin, which causes phosphorylation of myosin light chain).
- Contraction is terminated in smooth muscle by a dephosphorylation process.

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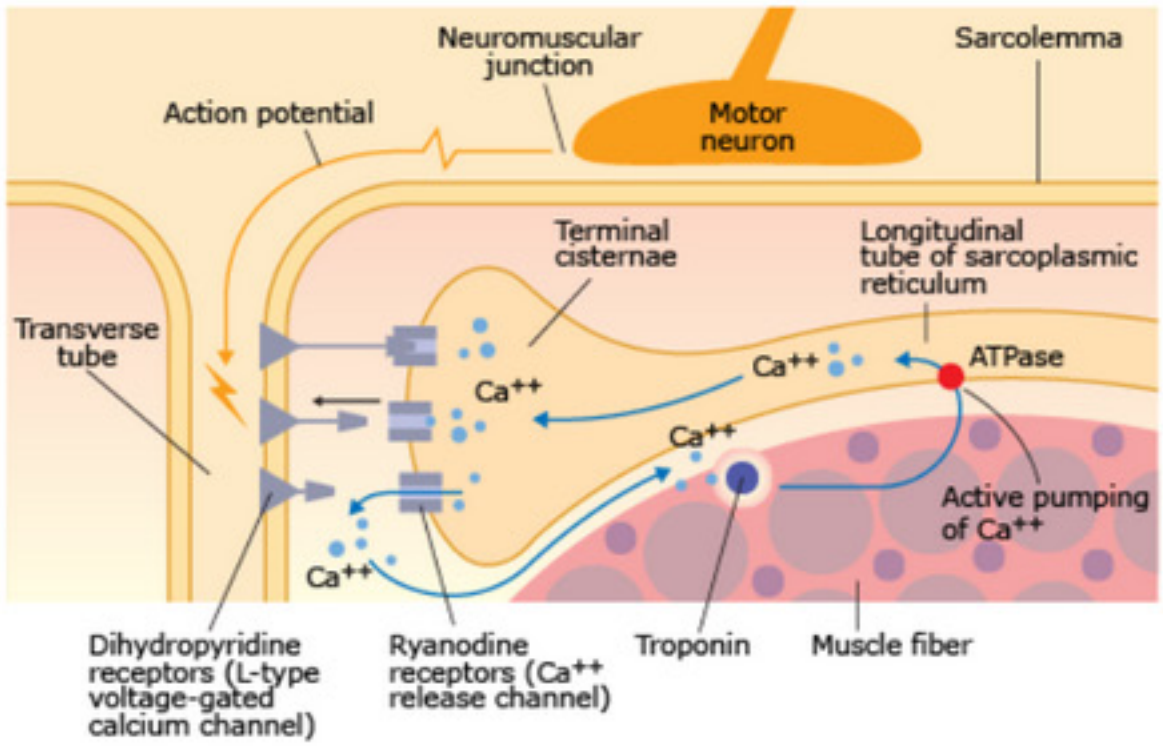
1 Skeletal Muscle



▲ **Figure 8–1.0** Excitation-Contraction Coupling: Skeletal Muscle

- Action potential initiated at the neuromuscular junction.
- Action potential spreads across the surface sarcolemma and down the T tubular membranes, which are continuous with the surface membrane.
- T tubule penetrates deep within the cell and closely approximant the terminal cisternae of the sarcoplasmic reticulum which serve as a storage depot for Ca^{++}.
- The T tubular membrane contains L-type voltage-gated Ca^{++} channels referred to as dihydropyridine (DHP) receptors that activate, but no Ca^{++} influx occurs.
- The DHP receptors are in contact with and activate Ca^{++} release channels of the terminal cisternae known as *ryanodine receptors (RY)*.
- Activation of the RY receptors allows the passive release of Ca^{++} into the ICF myoplasm—now free Ca^{++}.
- Ca^{++} attaches to troponin to initiate mechanical contraction (cross-bridge cycling).
- Ca^{++} is actively pumped into the longitudinal tubules of the sarcoplasmic reticulum by a Ca^{++}ATPase to terminate mechanical contraction (cross-bridge cycling).
- Ca^{++} is transported within the sarcoplasmic reticulum back to its primary storage depot in the terminal cisternae.

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1.1 Important Points

- Contraction is initiated by the passive release of Ca^{++} from the sarcoplasmic reticulum, but actively returned to terminate contraction.
- Two ATPases take part in contraction:
  - ATPase of the cross-bridge head that supplies energy for the power-stroke and the development of active tension during contraction.
  - ATPase of the sarcoplasmic reticulum terminates contraction (calcium-dependent ATPase or SERCA-sarcoplasmic endoplasmic reticulum calcium ATPase).
- Only internally cycled Ca^{++} takes part in contraction. No ECF Ca^{++} involved.

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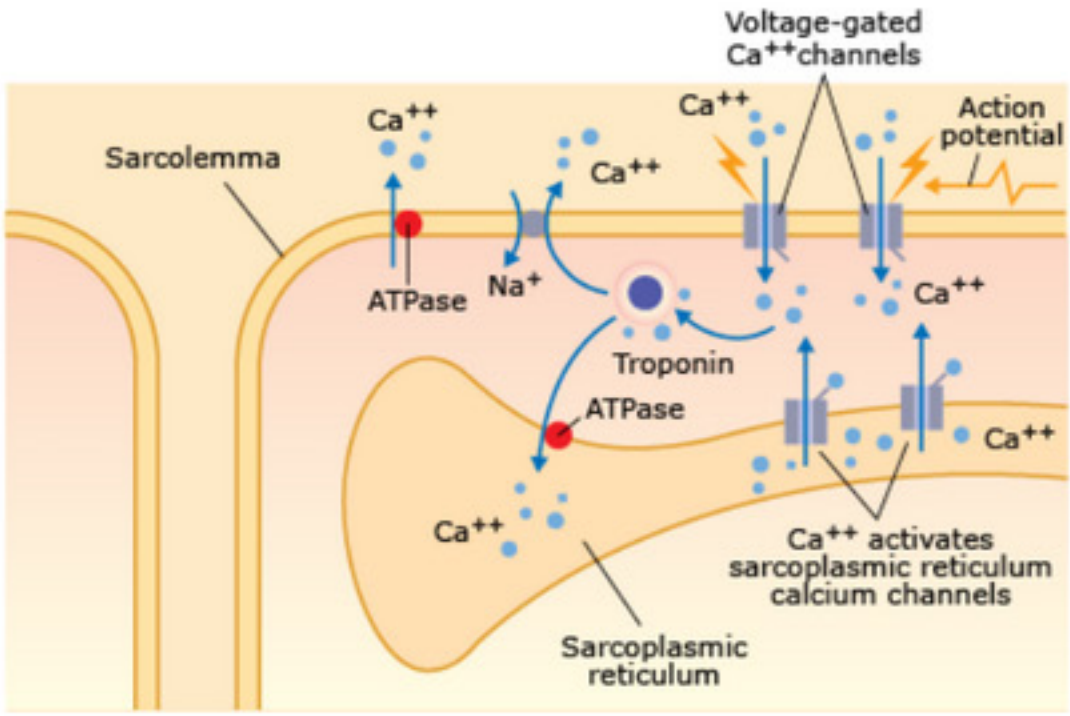
2 Cardiac Muscle



▲ **Figure 8–2.0** Excitation-Contraction Coupling: Cardiac Muscle

- Action potential spreads from cell to cell across the surface of the sarcolemma via gap junctions.
- Sarcolemma contains L-type voltage-gated calcium channels that slowly activate and slowly inactivate.
- Ca^{++} diffuses from the ECF into the ICF.
- Free ICF Ca^{++} activates calcium-gated calcium channels (ryanodine receptors, calcium release channels) of the sarcoplasmic reticulum.
- Diffusion of Ca^{++} from the sarcoplasmic reticulum to the myoplasm.
- Both the Ca^{++} diffusing into the cell (one third) and the Ca^{++} diffusing through the calcium release channels (two thirds) attach to troponin to initiate contraction.
- Contraction is terminated by the active removal of Ca^{++} by two mechanisms:
  - The calcium-dependent ATPase of the sarcoplasmic reticulum.
  - The secondary active transport of Ca^{++} from the ICF to the ECF.
- A calcium-dependent ATPase of the sarcolemma membrane plays a minor role in removing the free ICF calcium.

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2.1 Important Points

- Ca^{++} diffusing through the L-type calcium voltage-gated channels is often referred to as trigger Ca^{++}. If no trigger Ca^{++} enters the cell during the action potential plateau, there is no mechanical contraction (heart stops in diastole).
- If, under experimental conditions, too much Ca^{++} enters the cell from the ECF and the Ca^{++} removal mechanisms are overwhelmed (maintenance of high free ICF Ca^{++}), the heart will tetanize (heart stops in systole).
- Calcium channel blockers reduce the entry of trigger Ca^{++} and reduce the force of contraction.
- Digitalis reduces the removal of free Ca^{++} by the secondary active transport process (↓ Na/K-ATPase pump) so that more is removed and stored in the sarcoplasmic reticulum.
- The amount of sarcoplasmic reticulum Ca^{++} released by the trigger Ca^{++} is dependent on the amount stored. Therefore, digitalis causes more sarcoplasmic reticulum calcium to be involved in contraction and increases the magnitude of the mechanical response.
- Sympathetic stimulation activates β_1 receptors of the sarcolemma to increase intracellular cAMP.

  Increased cAMP has two main effects:

  - Increases the inflow of trigger Ca^{++} through the L-type Ca^{++} channels.
  - Increases the activity of sarco/endoplasmic reticulum Ca^{++}-ATPase (SERCA), and more Ca^{++} is stored in the sarcoplasmic reticulum and less extruded via secondary active transport; therefore, more released during a given action potential.

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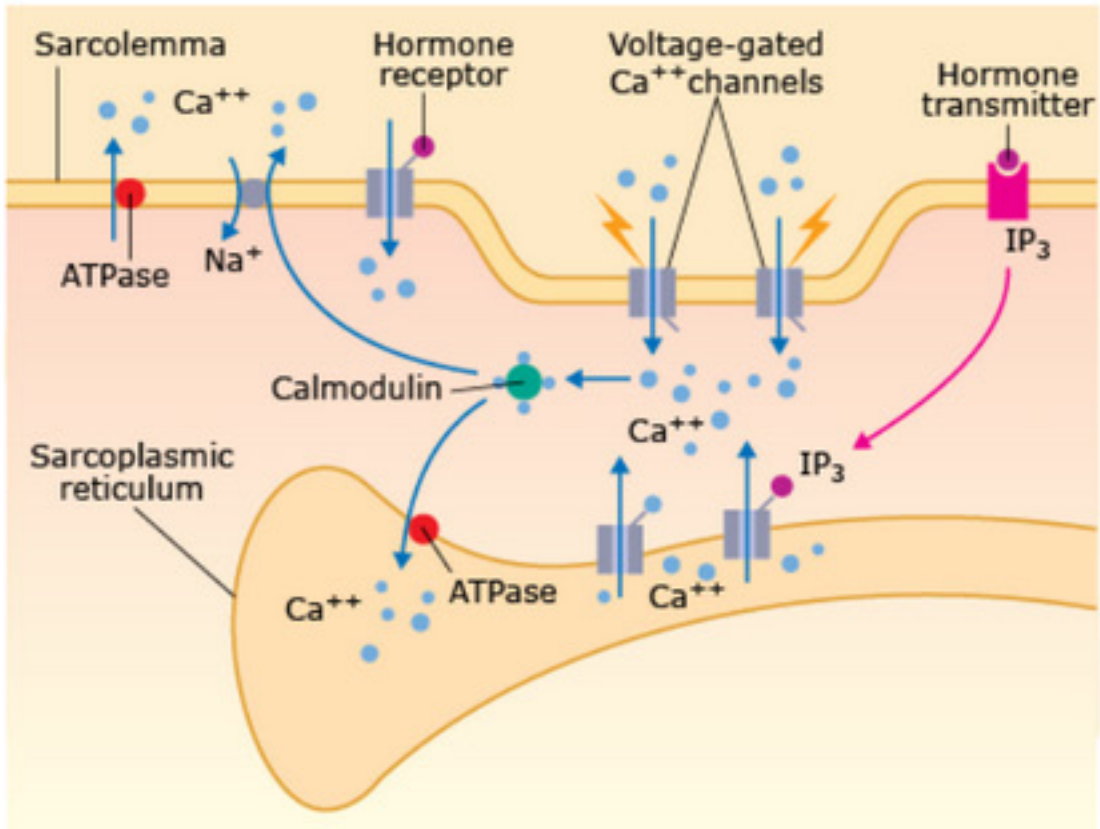
3 Smooth Muscle



▲ **Figure 8–3.0** Excitation-Contraction Coupling: Smooth Muscle

- No T tubules in smooth muscle; instead, the surface membrane has depressions (caveolae) that in some ways could be considered analogous to T tubules in skeletal muscle.
- L-type voltage-gated calcium channels are associated with the caveolae.
- Small gap between caveolae and the sarcoplasmic reticulum membrane stores of Ca^{++}.
- Ryanodine receptor calcium release channels associated with the sarcoplasmic reticulum.
- Sarcolemma also contains ligand-gated calcium channels activated by neurotransmitters and hormones.
- Influx of ECF Ca^{++} triggers the release of Ca^{++} from the sarcoplasmic reticulum, which attaches to calmodulin to initiate mechanical contraction.
- Contraction is terminated by the active removal of Ca^{++} by two mechanisms:
  - The calcium-dependent ATPase of the sarcoplasmic reticulum.
  - The secondary active transport of Ca^{++} from the ICF to the ECF.
- In addition, the sarcolemma contains hormone receptors that, when activated by various substances, generate ICF inositol 1,4,5-triphosphate (IP3 second messenger), which has receptor-gated calcium channels in the sarcoplasmic reticulum.
- Sarcolemma has inhibitory receptors acting through cAMP and cGMP that inhibit contraction.

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3.1 Summary

- Action potential can activate L-type voltage calcium channels. Influx of trigger Ca^{++} activates calcium-gated calcium release channels of the sarcoplasmic reticulum.
- Action potentials can be generated by stretching smooth muscle.
- Ligand-gated calcium channels in the sarcolemma can also allow influx of trigger calcium.
- Neurotransmitter- and hormone-mediated sarcolemma receptors, when activated, can generate IP3. There are IP3-gated calcium channels in the sarcoplasmic reticulum.
- Other sarcolemma receptors for transmitters and hormones are inhibitory and decrease the force of contraction. Second messengers include cAMP and GMP.

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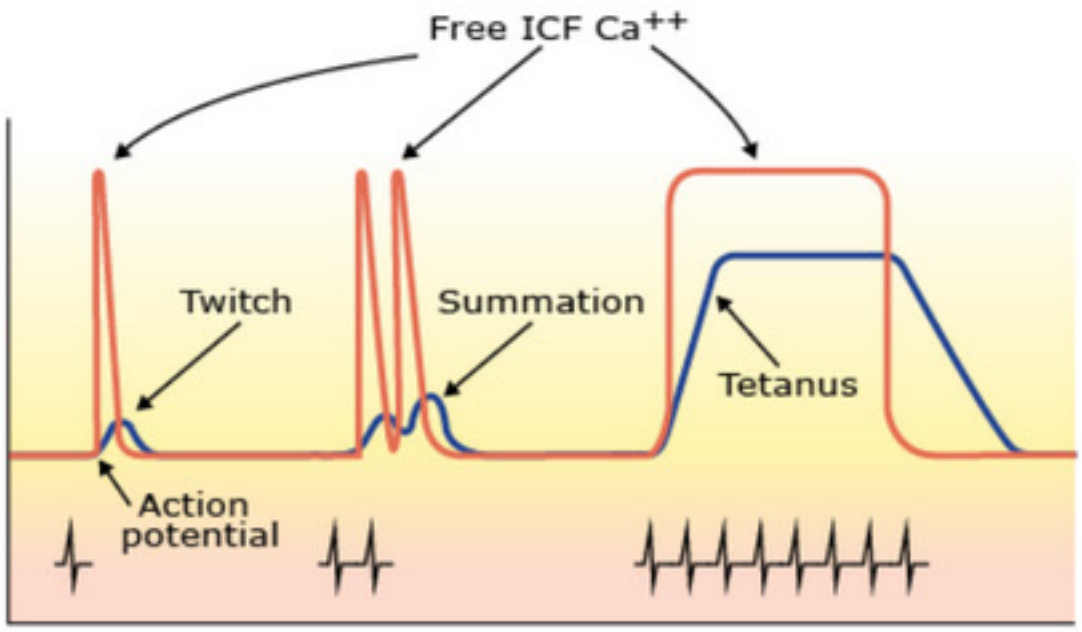
4 Electrical–Mechanical Coupling: Skeletal vs. Cardiac Muscle

4.1 Skeletal Muscle



▲ **Figure 8–4.1** Effect of AP Frequency on Skeletal Muscle Mechanical Response

- Action potential releases a pulse of Ca^{++} from the sarcoplasmic reticulum sufficient to initiate all the cross-bridges to cycle.
- Much of the Ca^{++} is quickly removed before it can participate in contraction. The Ca^{++} that does participate causes a mechanical muscle twitch.
- Because the duration of the action potential is shorter than the mechanical response, a second action potential, releasing a second burst of Ca^{++}, increases the Ca^{++} activated troponin, more cross-bridges cycle, and a greater mechanical response is achieved.
- A high-frequency train of action potentials releases Ca^{++} at a rate faster than it can be removed, saturating the troponin for a significant duration.
- There is then fusion of the mechanical response, which is tetanus.

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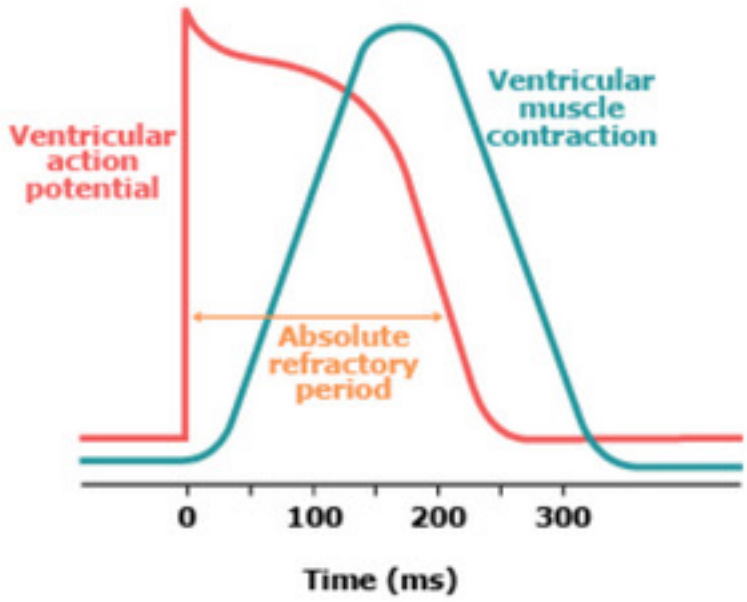
4.2 Cardiac Muscle



▲ **Figure 8–4.2** Ventricular Muscle Contraction: Electrical vs. Mechanical Duration

- In cardiac muscle, the duration of the action potential is much longer than in skeletal muscle.
- The duration of the action potential and the duration of the mechanical response are similar.
- Because the absolute refractory period is almost as long as the mechanical contraction, only one pulse of free Ca^{++} is available per mechanical event.
- It is not possible to create tetanus in cardiac muscle under natural conditions.

Note: It is important to understand why it is possible to create tetanus in skeletal muscle under *in vivo* condition but not possible with heart muscle.

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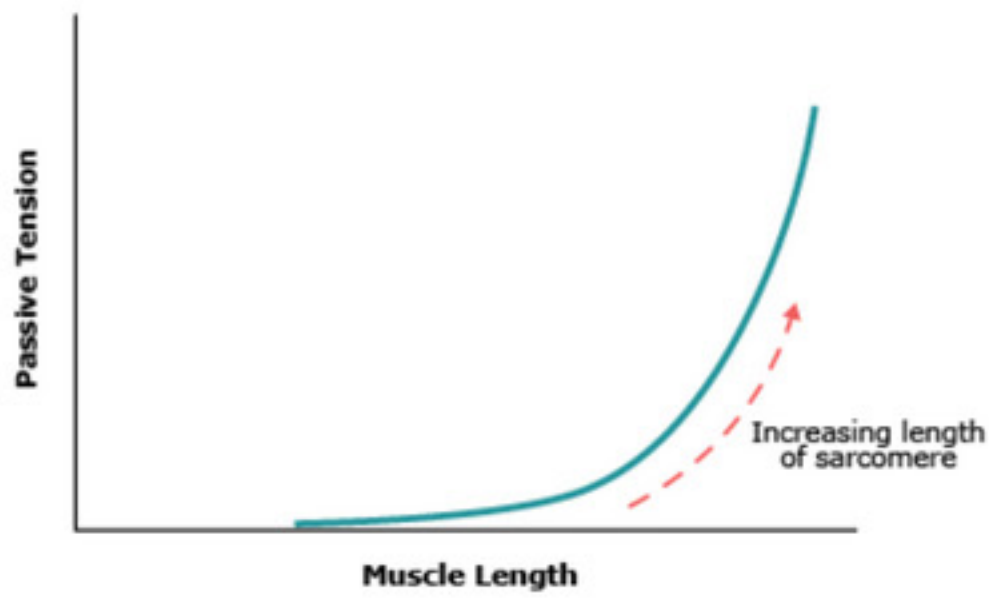
1 Length-Tension Relationships

1.1 Preload

- When a relaxed muscle is stretched, the elastic elements resist that stretch and the muscle develops a passive tension.
- Passive tension gradually increases at first (compliant range); then, more rapidly as tension increases (stiff range).
- Pre-stretching the muscle also pre-stretches the sarcomere and alters the overlap of the actin and myosin filaments.
- Preload can be considered a pre-stretch of the sarcomeres.



▲ **Figure 9–1.1** Effect of Preload on Muscle Length and Tension

1.2 Afterload

- When a muscle contracts, cross-bridges cycle, the sarcomere shortens and, in doing so, generates an active pull or tension on the tendons.
- The total force or tension developed during contraction (isometric phase) is the passive or pre-stretch force plus the active force.
- This total force attempts to lift a load.
- Afterload is the total force developed by the muscle during contraction necessary to lift the load.
- Because of leverage, to lift a 10 lb weight, the biceps may have to generate a larger force, say 18 lbs. The afterload is then 18 lbs.
- With the left ventricle, the afterload is the total force that muscle mass must generate to start moving blood into the aorta: the force necessary to open the aortic valve.

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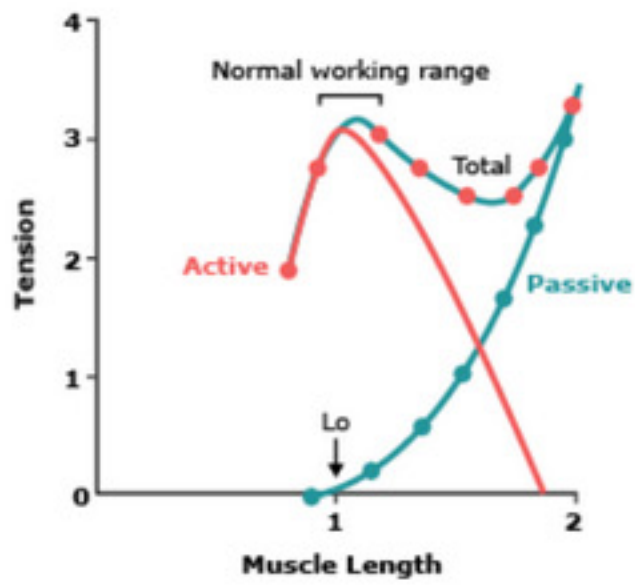
1.3 Summary

- Preload is the prestretch of the sarcomere. This generates passive tension.
- Contraction is the cycling of the cross-bridges, which creates an active force on top of the passive force.
- Afterload is the total force the muscle must generate to lift a load.

1.4 Preload vs. Active Force

- In a classic demonstration using isolated muscle, at various prestretches of the sarcomere, an isometric tetanic contraction is then induced.
- In a tetanic contraction, the troponin is saturated with Ca^{++} and all the cross-bridges that can cycle will be cycling.
- The magnitude of the active force generated is proportional to the number of cross-bridges cycling.
- The graph generated shows:
  1. The prestretch or preload curve that develops passive tension.
  2. The active tension developed during tetanus.
  3. The total tension developed (active plus passive).



▲ **Figure 9–1.4** Length-Tension Relationships for an Isometric Contraction

1.5 Conclusions

- At first, the greater and greater pre-stretches of the muscle (sarcomere) generate a greater and greater active tension during the isometric contraction.
- A small range of prestretches generates the greatest active tension. This range is referred to as L_o (sarcomere lengths 2.0 to 2.2 μ): the optimal length of the sarcomere where the greatest numbers of cross-bridges are cycling.
- If the muscle is prestretched beyond L_o, the active force declines.
- The active tension curve is a bell-shaped curve. It has an ascending limb, a peak region, and a descending limb.
- This phenomenon, in which the prestretch of the sarcomere alters the magnitude of the active force, is known as the Frank-Starling mechanism. It was originally observed in cardiac muscle.

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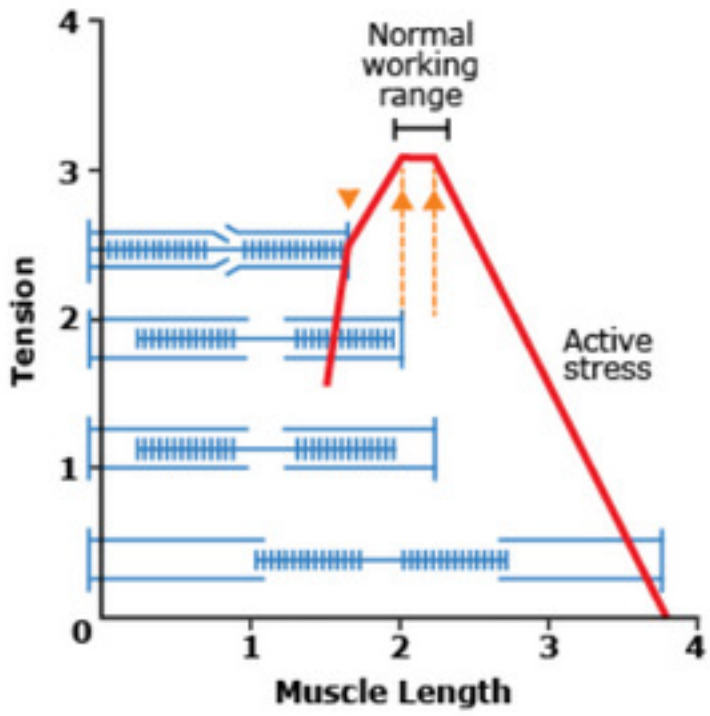
2 Sarcomere Length vs. Cross-Bridge Cycling

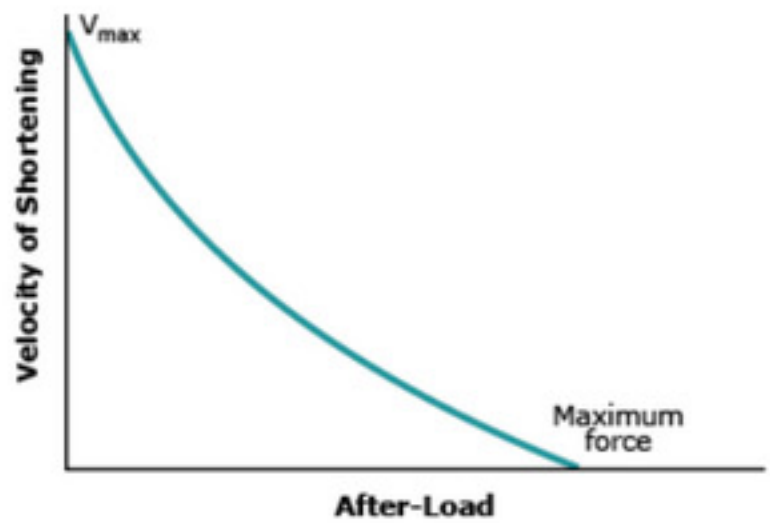
- Within the L_o range, there is the ideal alignment of the actin and myosin, and all the cross-bridges can potentially cycle.
- A prestretch beyond L_o decreases the overlap between the actin and myosin, and thus, fewer cross-bridges can cycle.
- A prestretch below L_o causes a displacement of the actin and myosin, and fewer cross-bridges are able to cycle.
- Skeletal muscle in vivo is pre-stretched close to L_o. Therefore, a maximal activation of the muscle generates the greatest force possible.



▲ **Figure 9–2.0** Sarcomere Length vs. Active Tension for an Isometric Contraction

3 Force-Velocity Relationships: In Vivo Muscles at L_O

- Maximum velocity of shortening (V_{max}) is developed in the absence of afterload.
- V_{max} is the maximum cycling rate of the cross-bridges and is determined by the rate of energy utilization (ATPase activity).
- Maximum active force is determined by the number of cross-bridges cycling=muscle mass or the number of motor units activated.
- White skeletal muscle can generate the greatest V_{max} and the greatest active force.



▲ **Figure 9–3.0** Force Velocity Relationship

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1 Introduction

In cardiac, as with skeletal muscle, the active force generated during contraction is proportional to the number of cross-bridges that are cycling in the muscle mass. The more cross-bridges that cycle, the greater the force of contraction. In cardiac muscle, we generally consider two, somewhat separate, factors that contribute to the overall force of contraction:

- The preload factor, also known as the Frank-Starling mechanism.
- The contractility factor, which, under acute conditions, is calcium dynamics.

Note: The active force generated by the myocardium during systole depends on the preload factor and the contractility factor.

1.1 Ventricular Preload

- The increased stretch induced in the sarcomere during increased diastolic filling of the ventricle results in an increased force of contraction (Frank-Starling mechanism).
- Unlike skeletal muscle that operates close to L_o, cardiac muscle operates on the *ascending limb* of the active tension curve.
- In its normal operating range, the ventricle is a very compliant structure, but as preload increases, it quickly stiffens, keeping it on the ascending limb. The pericardium, being stiff acutely, also assists.
- The stretch-induced increase in the force of contraction differs significantly from the experimental observations in skeletal muscle.
- Titin, a very elastic protein, may play a role during increased preload by reducing the distance between the actin and myosin, increasing the interaction of the filaments.
- Stretching the myocardium also increases the sensitivity of the contractile machinery to Ca^{++}. In other words, the L_o concept as explained for skeletal muscle does not strictly apply to cardiac muscle.

1.2 Summary

The Frank-Starling mechanism is an inherent property of the myocardium itself that attempts to match venous return with cardiac output. It is dependent upon the ventricular chamber being a very compliant structure in its normal operating range. If muscle compliance decreases (becomes stiffer), the Frank-Starling effect is diminished. This is referred to as *diastolic dysfunction*.

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1.3 Indices of Preload for the Left Ventricle

- Left ventricular end-diastolic volume
- Left ventricular end-diastolic pressure
- Left atrial pressure
- Pulmonary venous pressure
- Pulmonary wedge pressure

Pulmonary wedge pressure is measured via a Swan-Ganz catheter wedged in a small pulmonary artery with the tip pointing downstream toward the left atrium. The same sequence could be developed for the right ventricle: Right atrial pressure and systemic venous pressure are indices of preload on the right ventricle.

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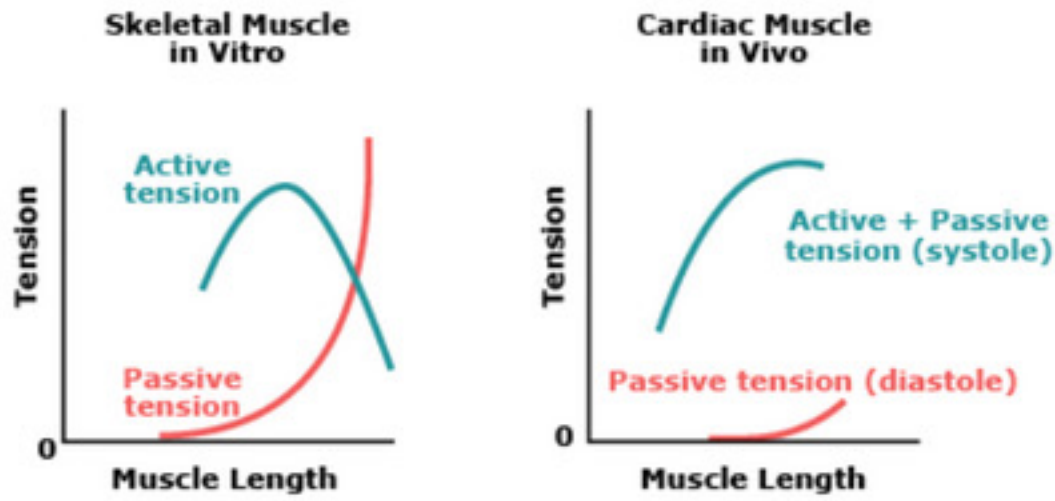
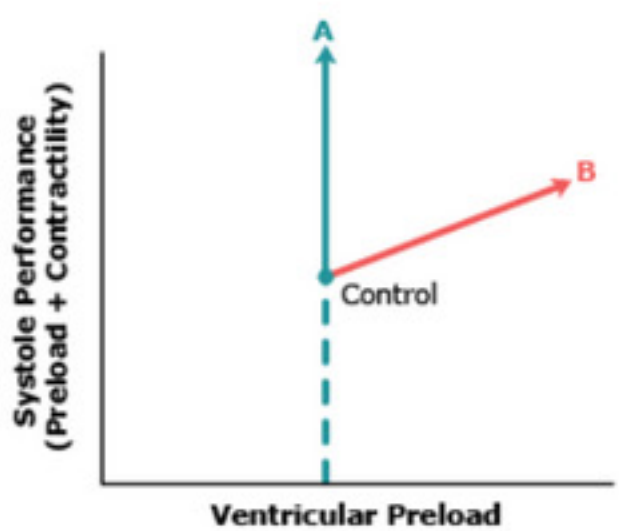
2 Skeletal vs. Cardiac Muscle Mechanics



▲ **Figure 10–2.0** Skeletal vs. Cardiac Muscle Mechanics

2.1 Contractility

- Sympathetic stimulation of myocardial β_1 receptors results in an increased force of contraction (increased systolic performance) because more free Ca^{++} participates in contraction.
- More free Ca^{++} means more cross-bridges will cycle.
- In addition, sympathetics speed Ca^{++} dynamics; it becomes active faster and Ca^{++} is removed faster to terminate systole.
- Digitalis (as mentioned earlier) causes similar changes in Ca^{++} dynamics.
- Acute changes in contractility are usually due to changes in Ca^{++} dynamics.
- Chronic changes in contractility involve other mechanisms. In low-output heart failure, the decreased systolic performance of the ventricle is due to myocyte dysfunction.
- Since it is preload plus contractility that determines systolic performance of the ventricle, if a change in performance is not due to preload, it must be due to a change in contractility. This is illustrated in the figure below.



▲ **Figure 10–2.1** Systolic Force: Preload vs. Contractility

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- The control point represents the initial level of systolic performance at a given preload.
- If preload increased, the next ventricular systolic performance is B. The increase in performance is Frank-Starling, contractility unchanged.
- If instead, there is additional β_1 activation, ventricular performance during the next systole is A. The increased performance at the same preload means it was achieved by an increased contractility.
- A change in performance at a given preload means a change in contractility. For example, hypertension requires an increased ventricular systolic performance (increased force of contraction) to eject the stroke volume. In the early stages of essential hypertension, this is achieved at a normal preload. Thus, the increased performance is due to maintaining an elevated level of contractility.

2.1.1. Summary

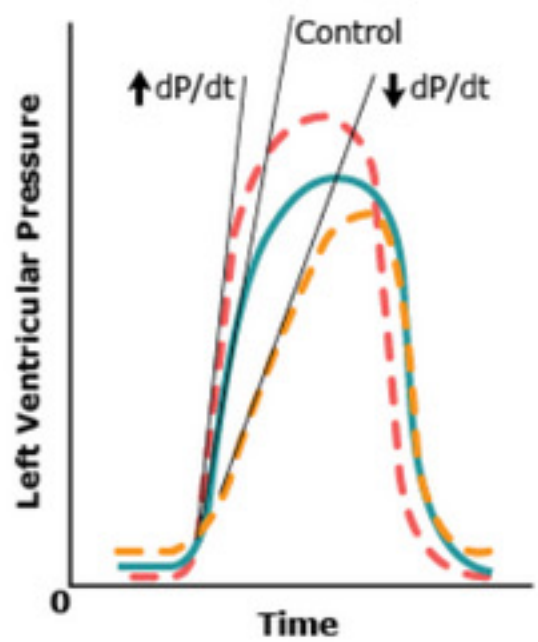
Contractility is an extrinsically regulated factor affecting myocardial performance. It is under nervous control, and the output is mainly sympathetic. If sympathetic stimulation cannot maintain an adequate systolic performance of the ventricle, this is referred to as *systolic dysfunction*.

2.2 Indices of Contractility

There are three common indices of contractility:

1. Maximal dP/dt during isovolumetric contraction:

- The slope of the tangent line to the pressure-time curve is the old experimental index of contractility.
- ↑ slope = ↑ contractility.
- ↓ slope = ↓ contractility.
- Slope is a function of Ca^{++} dynamics during systole.
- Preload sensitive, not afterload sensitive.



▲ **Figure 10–2.2** dP/dt as an Index of Contractility

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2. Peak aortic velocity during ventricular ejection:

- An index of contractility, but afterload sensitive.
- Increased velocity = increased contractility.

3. Ejection Fraction:

- Usually presented as the percentage of the ventricular volume ejected during systole.
- This has become a standard index of contractility.
- Ejection fraction (EF) = stroke volume (SV)/end diastolic volume (EDV) 55–60%, fairly normal.
- ↑ contractility = ↑ EF.
- ↓ contractility = ↓ EF.
- Afterload sensitive ↑ Afterload = ↓ EF.

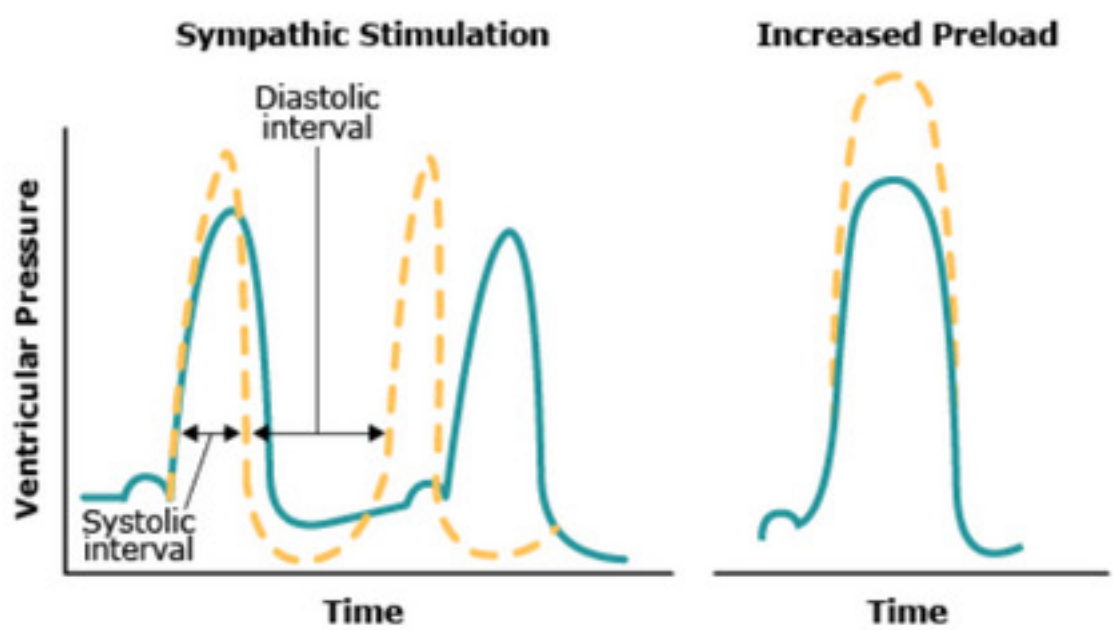
Note: In the early stages of hypertension, there is an increased performance at a normal preload, thus, there must be an increased contractility. However, there is no increase in EF. Hypertension reduces the EF. In most cases, EF remains in the normal range.

2.3 Sympathetic Stimulation vs. Preload on Left Ventricular Dynamics

	Sympathetic Stimulation	Preload
dP/dt	↑	–
EF	↑	–
Rate relaxation	↑	–
Systolic interval	↓	–
Systolic pressure	↑	↑

The ↑ HR that accompanies sympathetic stimulation will ↓ the ventricular diastolic interval.

Generalization: Contractility determines the ventricular systolic interval; heart rate determines the diastolic interval.



▲ **Figure 10–2.3** Ventricular Systolic and Diastolic Interval: Effect of Preload vs. Contractility

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2.4 Afterload

- Impedance that the ventricle must overcome to eject a stroke volume.
- Can be considered the overall force the ventricular muscle must develop to begin ejecting a stroke volume.
- The best index is the ventricular pressure needed to begin a stroke volume.
- For the left ventricle, it is the pressure needed to open the aortic valve. This is equivalent to diastolic blood pressure.
- Diastolic blood pressure is the best clinical index of afterload on the heart.
- Diastolic blood pressure is mainly determined by the resistance of the arterioles. Thus, afterload is a function of total peripheral resistance (TPR).
- Vasodilation ↓ TPR and ↓ afterload; vasoconstriction ↑ TPR and ↑ afterload.
- Other indices of afterload include mean aortic pressure, ventricular wall tension during systole.

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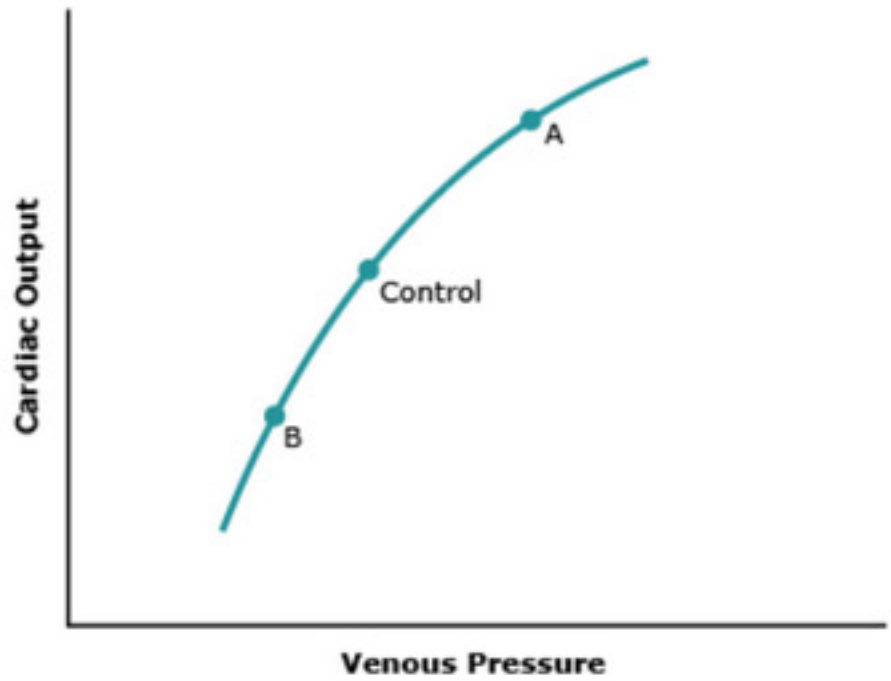
3 Ventricular Function Curves

- Constructed by keeping contractility constant and following ventricular performance as preload increases. Thus, all points on a curve have the same contractility.
- Represents the ascending limb of the active tension curve and assesses the Frank-Starling effect.
- X-axis: An index of preload; end-diastolic volume or pressure, atrial pressure, venous pressure.
- Y-axis: An index of the systolic performance of the ventricle; best indices assess the work of the heart, such as CO × BP, stroke work, stroke power. Cardiac output could also be used as an index of overall performance.

3.1 Single Cardiac Function Curve



▲ **Figure 10–3.1** Cardiac Function Curve

Control → A:

- Increase in performance due to increased preload, contractility unchanged.

Control → B:

- Decrease in performance due to decreased preload, contractility unchanged.

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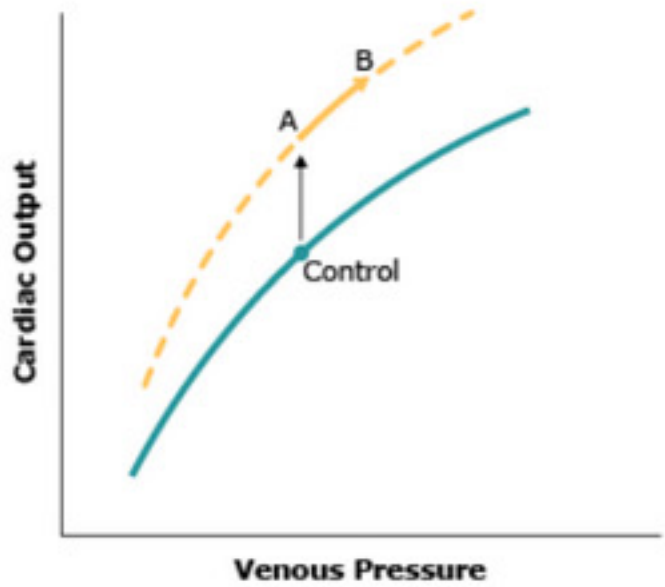
3.2 Essential Hypertension and Exercise



▲ **Figure 10–3.2** Cardiac Function Curves: Hypertension and Exercise

Control → A:

- Increase in performance at the same preload = increased contractility.
- Essential hypertension.
- Light to moderate exercise: The increase in venous return is mainly carried by an increased heart rate, and thus no dramatic changes in preload.

Point A → B:

- Moderate to very heavy exercise, just before exhaustion.
- The increased heart rate cannot keep up with the increased venous return, and preload increases.
- Increased performance due to increased contractility and increased preload.

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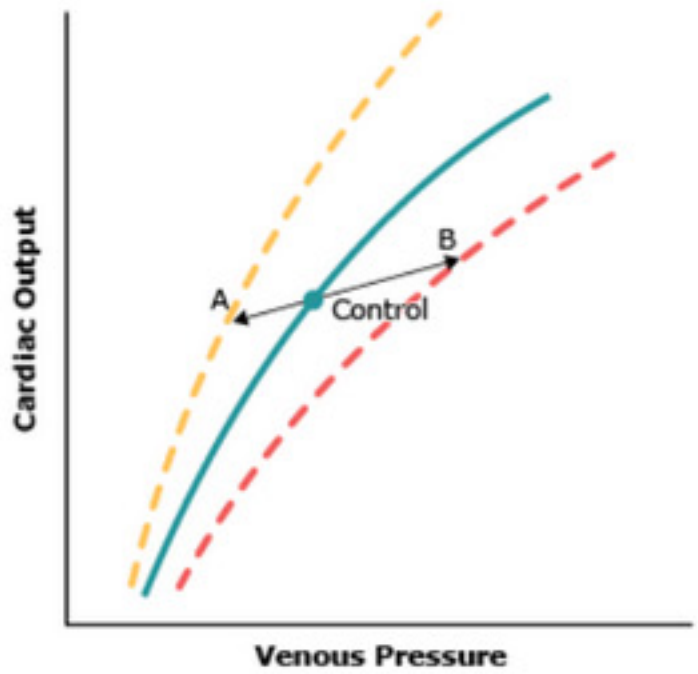
3.3 Changes in Circulating Volume



▲ **Figure 10–3.3** Cardiac Function Curves: Changes in Circulating Volume

Control → A:

- Loss of body fluid decreases venous return and ventricular filling in diastole, as in hemorrhage, diarrhea.
- Performance decreases due to decreased preload.
- Decreased cardiac output decreases blood pressure.
- To compensate, the carotid sinus reflex increases sympathetic stimulation.
- The increased contractility partially compensated for the loss in preload (also ↑ HR).

Control → B:

- Gain of body fluid increased venous return, as in transfusion.
- Performance increases due to increased preload.
- Increased cardiac output increases blood pressure.
- To compensate, the carotid sinus reflex decreases sympathetic stimulation.
- The decreased contractility partially compensated for the increased preload.
- More importantly, the increased blood pressure decreased heart rate.

Note: If, following a hemorrhage, an infusion of fluid is elevating blood pressure, the heart rate should decrease.

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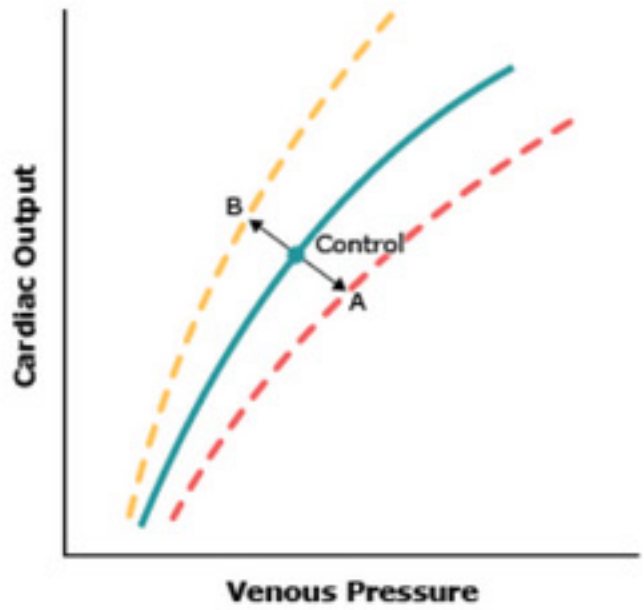
3.4 Changes in Contractility



▲ **Figure 10–3.4** Cardiac Function Curves: Changes in Contractility

Control → A:

- Performance decreases due to a loss in contractility, as in low-output heart failure.
- Decreased contractility decreases ejection fraction, increases end systolic volume and preload.
- The increased preload partially compensates for the loss of contractility.

Note: If the decreased ventricular performance leads to an inability to maintain blood pressure, there will be increased sympathetic activity overall and activation of the renin-angiotensin-aldosterone system (fluid retention).

Control → B:

- Performance increases due to an increase in contractility, as with digitalis.
- Increased contractility increases ejection fraction.
- Increased ejection fraction decreases preload.

Note: The figure does not take into account heart rate changes that affect preload, and as such, the decreased preload may not be a consequence of digitalis.

3.4.1 Summary

An increase in contractility shifts the cardiac function curve to the left, and it is a steeper curve. A decrease in contractility shifts the curve to the right, and it is a flatter curve. A decrease in preload or contractility usually results in an increase in the other factor to partially compensate. In most situations, preload and contractility move in opposite directions. Exceptions include: very heavy exercise and aortic insufficiency, where both contractility and preload increase.

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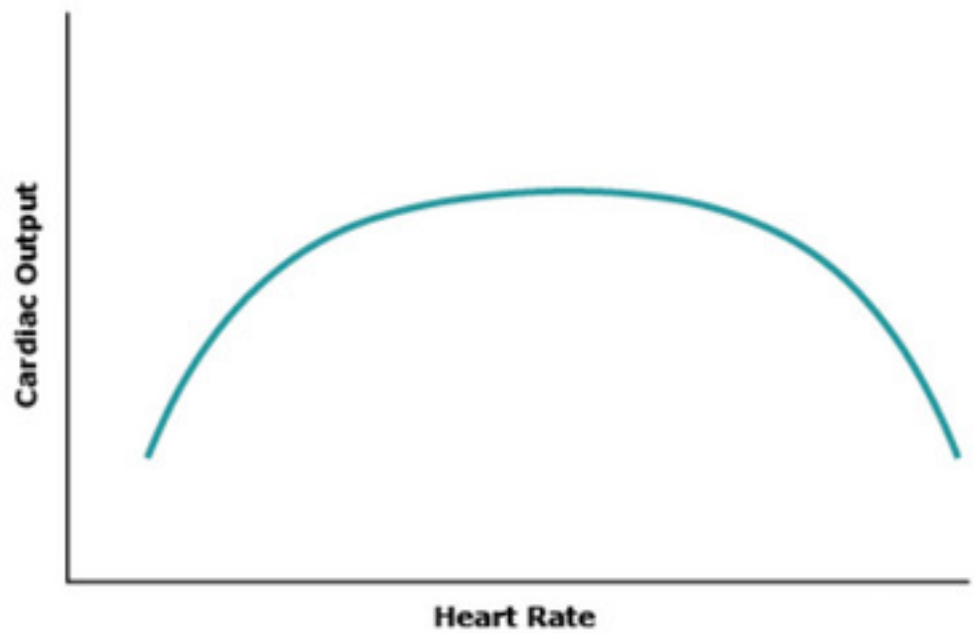
4 Heart Rate (HR) and Cardiac Output (CO)

CO = HR × SV (SV = stroke volume)

Cardiac output (L/min) in a steady-state is the same as venous return (L/min). If the heart cannot pump the venous return, it is, by definition, heart failure. There can be high-output and low-output heart failure. In both cases, there is venous pooling and a rise in venous pressure.

Under most conditions, heart rate is not a significant determinant of cardiac output. However, very high and very low heart rates decrease cardiac output. Many variables can affect venous return and cardiac output, and, as a consequence, there can be reflex changes, sympathetic and parasympathetic activity, and a change in heart rate is part of the response.

As shown in the following figure, a change in heart rate via a pacemaker has a minimal effect on cardiac output.



▲ **Figure 10–4.0** Heart Rate vs. Cardiac Output

↑ HR ↓ SV
↓ HR ↑ SV

If heart rate changes as an isolated variable, stroke volume changes in the opposite direction, with only minimal changes in cardiac output.

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Unit 4

The Circulation

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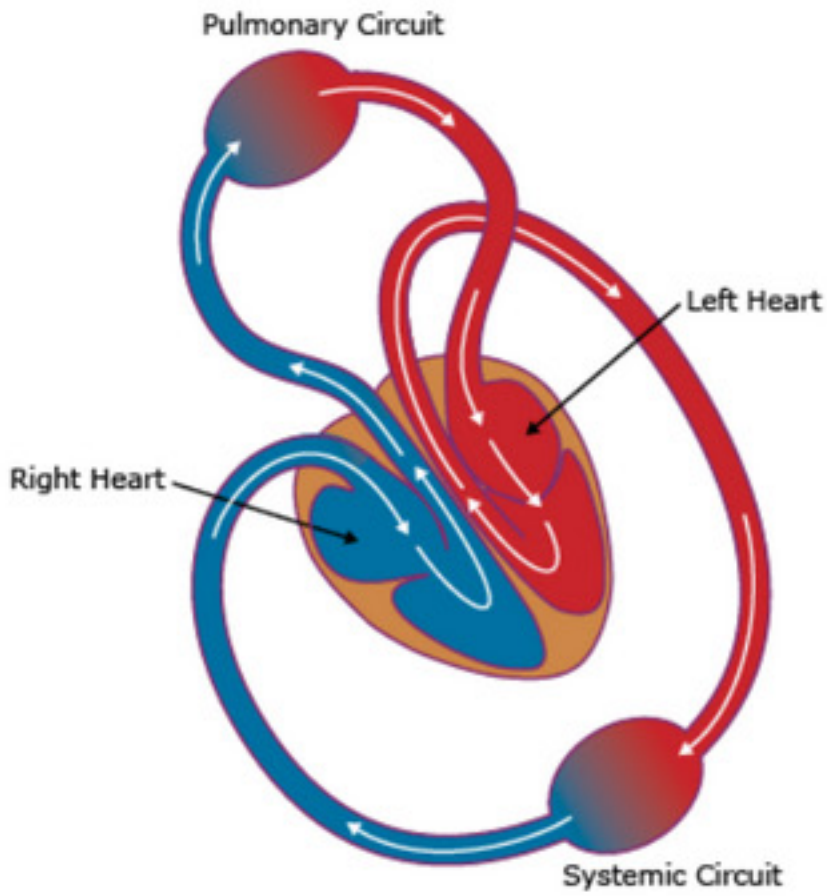
1 Introduction



▲ **Figure 11–1.0** Pulmonary and Systemic Circuits

- Pulmonary and systemic circuits are connected in series.
- In a series system, flow must be equal at all points.
- Pulmonary venous PO_2 = left heart PO_2 = systemic arterial $PO_2 \approx 100$ mmHg.
- Systemic venous PO_2 = right heart PO_2 = pulmonary arterial $PO_2 \approx 40$ mmHg.

1.1 Pulmonary vs. Systemic Circuit

	Pulmonary Circuit	Systemic Circuit
Arterial pressure	25/8, mean 15 mmHg	120/80, mean 92 mmHg
Atrial pressure	right = 2–4 mmHg	left = 4–7 mmHg
Ventricular pressure	right = 25/1–3 mmHg	left = 120/< 10 mmHg
Pressure gradient	10 mmHg	89 mmHg
Flow (CO)	5 L/min	5 L/min
Resistance	↓↓↓	↑↑

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2 Pulmonary Circuit

- Blood volume at rest ≈ 500 ml.
- Pulmonary arteries and veins are thin-walled, compliant tubes that act as a major blood reservoir.
- The pulmonary circuit filters systemic venous blood, preventing emboli from reaching the systemic arteries.
- In this passive circuit, blood flow and pressure are not regulated.
- ↑ CO ↑ pulmonary arterial pressure (vessels stretch, recruitment of capillaries) ↑ blood volume ↓↓ resistance.
- Large changes in CO result in only small changes in pulmonary pressures.
- Exercise: ↑↑↑ CO ↑ pulmonary pressures ↓↓ resistance ↑ blood volume and recruitment of capillaries.
- Hemorrhage: ↓↓↓ CO ↓ pulmonary pressures ↑↑ resistance ↓ blood volume.
- Pulmonary arteries and veins are sensitive to changes in pleural pressure.
- Inspiration: ↓ pleural pressure and vessel dilation, ↑ venous return to the right heart ↑ blood volume ↓ venous return to left heart ↓ BP ↑ HR.

  Expiration: ↑ pleural pressure and vessel compression, ↓ venous return to the right heart ↓ blood volume ↑ venous return to left heart ↑ BP ↓ HR.
- Valsalva maneuver: ↑↑ pleural pressure and severe vessel compression, ↓ venous return to the right heart ↓ blood volume ↑ venous return to left heart ↑ BP ↓ HR. This is followed by a decrease in blood pressure because of the severe compression of the pulmonary vasculature.
- Pulmonary capillaries are sensitive to changes in alveolar pressure.
- Positive pressure breathing ↑ alveolar pressure during inspiration, compressing the pulmonary capillaries ↓ pulmonary capillary flow (CO).
- A ↓ in alveolar PO2 causes a local vasoconstriction (hypoxic vasoconstriction) and a ↓ in blood flow.

Summary: The pulmonary circuit is a high-flow, low-pressure, low-resistance, very compliant, passive system. Pulmonary arteries and veins are sensitive to changes in pleural pressure, whereas pulmonary capillaries are sensitive to changes in alveolar pressure.

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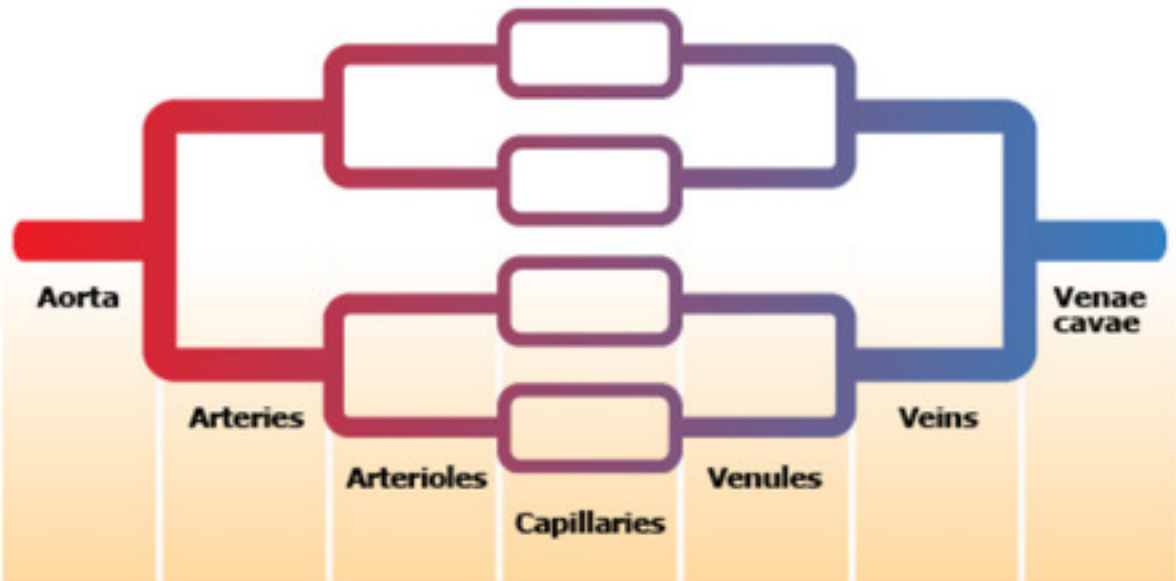
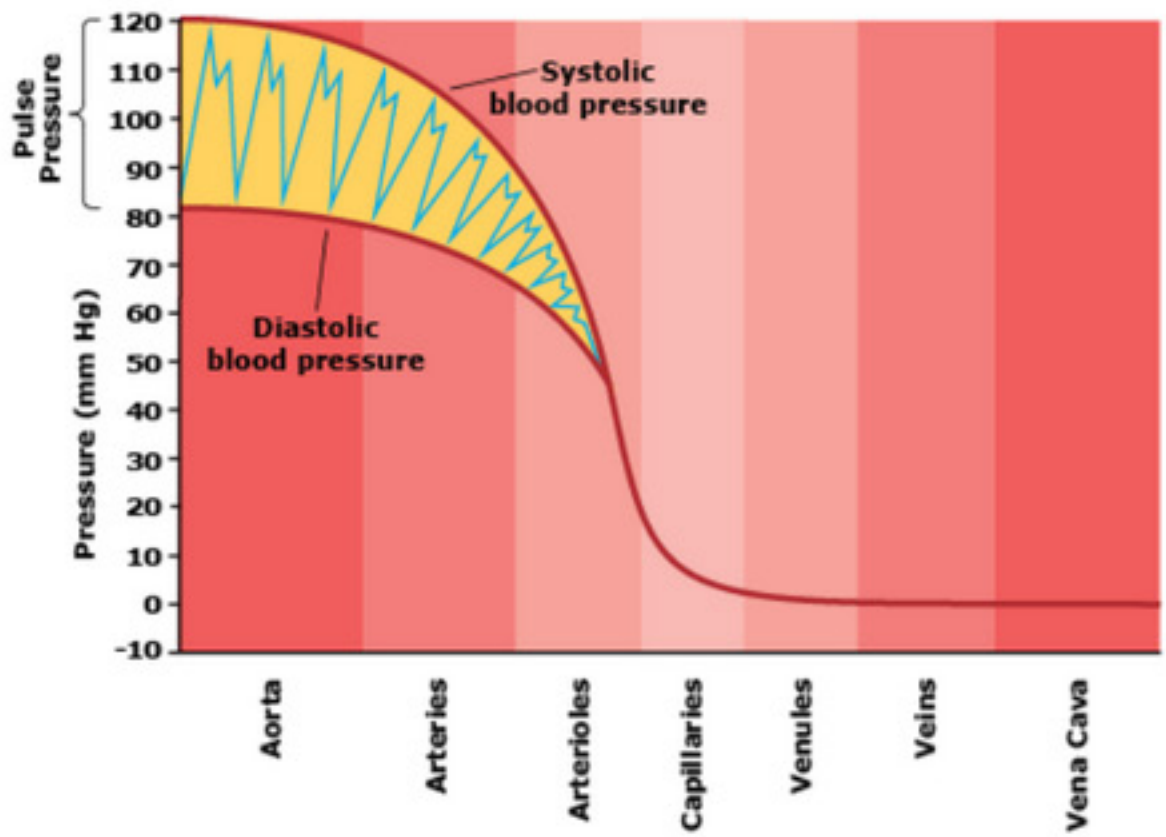
3 Systemic Circuit

3.1 Pressure



▲ **Figure 11–3.1A** Branching Systemic Circuit



▲ **Figure 11–3.1B** Pressures in the Systemic Circuit

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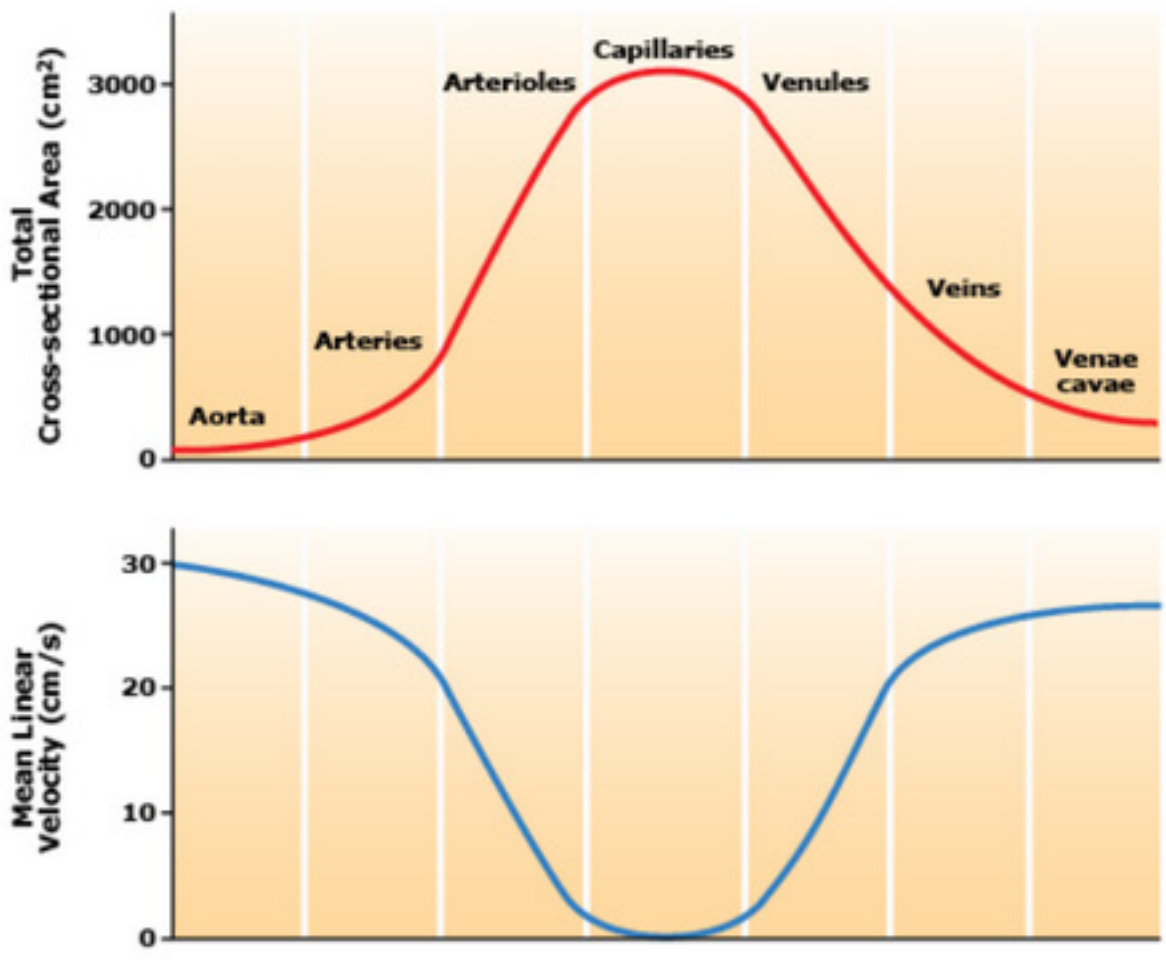
- In any hemodynamic system, pressure dissipates, overcoming the resistance of the system.
- The greater the resistance in a particular segment, the greater the loss in pressure.
- Systemic arteries: little decrease in pressure = low-resistance pathway.
- Systemic arterioles: greatest pressure decrease and dissipation of phasic pressure pattern = high-resistance pathway.
- Systemic veins: little decrease in pressure = low-resistance pathway.
- Dilation of an arteriole: ↓ resistance, ↑ flow, less pressure dissipation, ↑ capillary pressure.
- Constriction of an arteriole: ↑ resistance, ↓ flow, greater pressure dissipation, ↓ capillary pressure.
- The main factor determining capillary pressure is the resistance of the arterioles.

3.2 Velocity vs. Cross-Sectional Area

- In any hemodynamic system, there is always an inverse relationship between velocity and cross-sectional area.
- Velocity is speed (distance/time), not flow (volume/time).
- Aorta: smallest cross-sectional area = greatest velocity.
- Capillaries: greatest cross-sectional area = lowest velocity.
- The low velocity in the capillaries facilitates the exchange of nutrients and gases with the tissues.



▲ **Figure 11–3.2** Velocity vs. Cross-Sectional Area

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4 Hemodynamics

4.1 Poiseuille Equation

- The Poiseuille equation applies to steady laminar flow in rigid vessels, but the variables can approximate the cardiovascular system.

$$\text{Flow} = \frac{(P_1 - P_2)\pi r^4}{8\eta l}$$

$$\text{Flow} = \frac{P_1 - P_2}{R}$$

$$R = \frac{8\eta l}{\pi r^4}$$

Flow (volume/time) in a tube

P_1 = Pressure at the beginning of the system

P_2 = Pressure at the end of the system

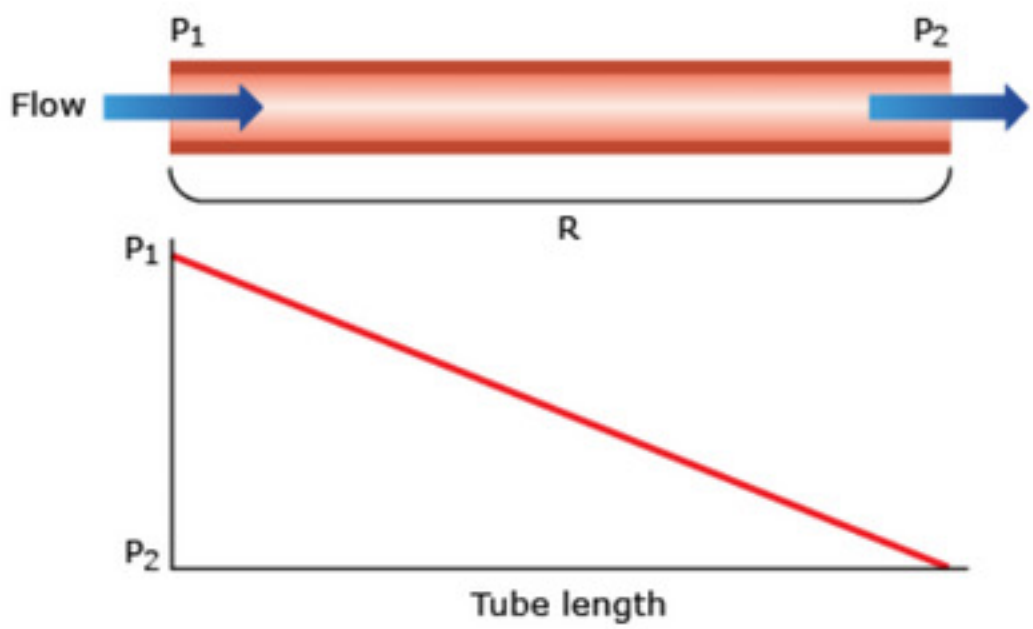
r = radius of the tube

l = length of the tube

η = viscosity of the fluid

R = resistance

- Flow in a single rigid tube.



▲ **Figure 11–4.1A** Flow in a Single Rigid Tube

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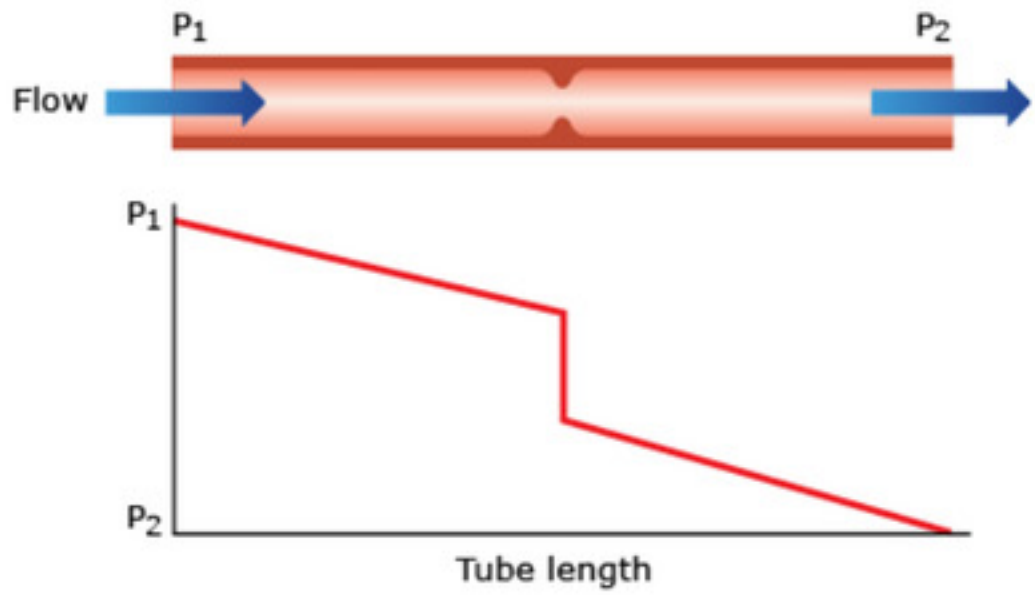
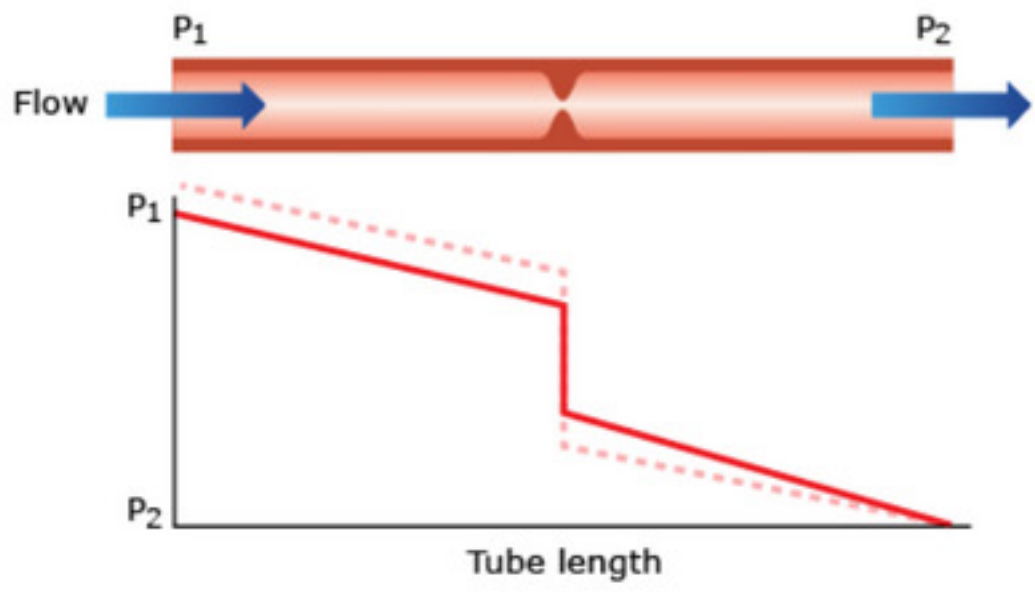
- For a tube of constant radius, pressure decreases uniformly between P_1 and P_2.



▲ **Figure 11–4.1B** A Point Resistance in a Single Tube

- Adding a resistance point in the middle of the system increases the overall resistance and flow decreases.
- Since pressure is lost overcoming resistance, a significant pressure drop occurs across the point resistance.



▲ **Figure 11–4.1C** Changing a Point Resistance in a Single Tube

- Increasing the resistance at the center point decreases the flow through that system and results in a greater drop across that point.
- Upstream, pressure increases, but downstream, pressure decreases.
- Applying this model to the systemic circuit, where P_1 = arterial pressure, P_2 = right atrial pressure, and the resistance point represents the arterioles:
  - Constricting the arterioles raises blood pressure, but decreases capillary pressure.
  - Dilating the arterioles decreases blood pressure, but increases capillary pressure.

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- Applying the Poiseuille equation to the systemic circuit, the following is true:

$$F = \frac{P_1 - P_2}{R}$$

F = cardiac output (CO)

P_1 = mean arterial pressure (MAP = 92 mmHg)

P_2 = right atrial pressure (RAP = 2 mmHg)

R = total peripheral resistance (TPR = mainly arterioles)

- Since RAP is very small compared to MAP, the equation can be simplified by ignoring this factor. Therefore:

$$CO = \frac{MAP}{TPR}$$

or

$$MAP = CO \times TPR$$

- This equation *now* states that only two factors determine mean blood pressure: *cardiac output* and the *resistance of the arterioles*.
- If cardiac output decreases, as it does in a hemorrhage, how can blood pressure be maintained close to normal?
  Answer: Arteriolar constriction
- If TPR decreases, as it does in exercise, why is there no significant change in blood pressure? *Answer:* There must be an equivalent increase in CO. If cardiac goes from a resting level of 5 L/min to 10 L/min during mild exercise, what must have happened to TPR?
  Answer: Decreased by 50%

Note: When applying the Poiseuille equation to the pulmonary circuit, P_2 cannot be ignored.

$$F = \frac{P_1 - P_2}{R}$$

F = cardiac output (CO)

P_1 = mean pulmonary arterial pressure (PAP = 15 mmHg)

P_2 = left atrial pressure (LAP = 5 mmHg)

R = pulmonary vascular resistance (PR)

$$CO = \frac{PAP - LAP}{PR}$$

- The Poiseuille equation is also used in determining the origin of pulmonary hypertension. With a Swan-Ganz catheter, cardiac output can be measured, along with PAP and LAP (pulmonary wedge pressure), permitting the use of the Poiseuille equation to calculate pulmonary vascular resistance.

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4.2 Resistance Factors

$$R = \frac{P_1 - P_2}{F} \qquad \frac{\text{mmHg (Pressure units)}}{\text{mL/min (flow units)}}$$

$$R \propto \frac{\eta l}{r^4}$$

η = viscosity of the fluid
l = length of the tube
r = radius of the tube

4.2.1 Blood Viscosity

- Viscosity is an internal property of a fluid that offers resistance to flow. It is the frictional force between the flowing fluid layers.
- The main determinant of blood viscosity is *hematocrit*.
- Polycythemia increases viscosity and TPR.
- Anemia decreases viscosity and TPR.

4.2.2 Tube Length

- Resistance is directly proportional to vessel length.
- Double the vessel length and resistance doubles.
- Decrease the vessel length by half and resistance decreases by half.

4.2.3 Tube Radius

- Of the three factors listed, the most important factor determining the resistance of a vessel is its radius.
- Resistance is inversely proportional to the fourth power of the radius.
- This means a very small change in radius causes a very large change in resistance.
- A slightly greater contraction of the smooth muscle surrounding an arteriole, decreasing very slightly the radius of the arteriole, creates a large increase in resistance.
- If the radius was decreased by 50%, resistance would increase 16 times.

Note: Tube radius is a much more important factor than length in determining resistance.

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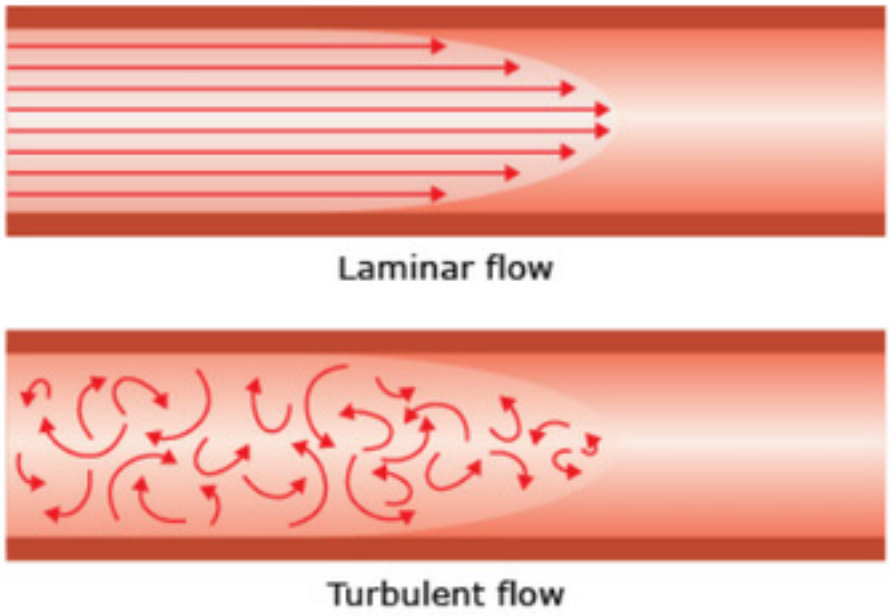
4.3 Laminar vs. Turbulent Flow



▲ **Figure 11–4.3** Laminar vs. Turbulent Flow

4.3.1 Laminar Flow

- Flow has layers of varying velocities: The layer next to the wall is motionless, and those near the center have increasing velocities, with the greatest at the center of the vessel.
- Laminar flow dominates the cardiovascular system outside the heart.
- Laminar flow is silent flow (no murmurs or *bruits*).
- A high-velocity layer close to the vessel wall creates a shearing wall stress, which is a force parallel to the wall. In some cases, this can damage the intima lining and allow blood to enter the media layer, creating a dissecting aneurysm; these most commonly occur in the ascending aorta of aging males, particularly those with a history of hypertension.

4.3.2 Turbulent Flow

- Disrupting the layers creates a turbulent flow in which the blood moves radially, as well as axially, forming eddies and vortices.
- Not only does this increase resistance, it results in a murmur or bruit.
- Thrombi are more likely to form in turbulent flow.

4.3.3 Reynolds Number

- Expresses the tendency of flow to become turbulent—the higher the Reynolds number, the greater tendency of the flow to become turbulent.

$$\text{Reynolds number } \alpha \quad \text{Tube diameter} \times \frac{\text{Velocity}}{\text{Viscosity}}$$

- Thus, large-diameter vessels and high-velocity, low-viscosity fluid promote turbulence, increasing the Reynolds number.

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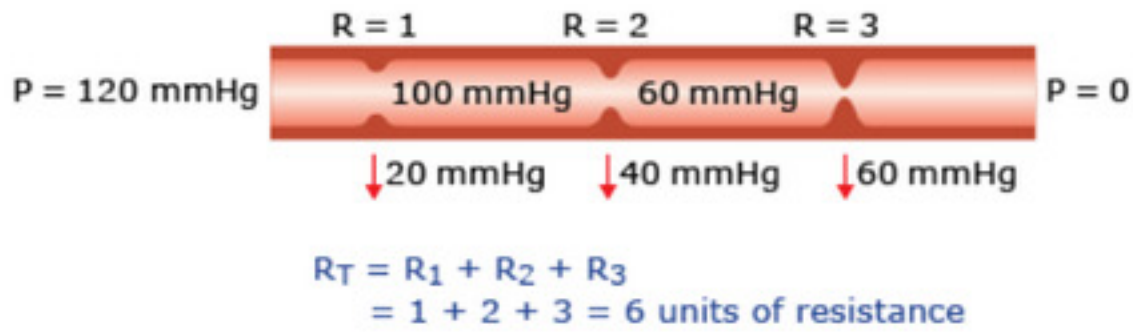
5 Series vs. Parallel Resistances

5.1 Series System

- Tubes connected end to end are connected in series.
- The flow must be the same at all points in a series system. If the flow at two points in a vascular system must always be the same, they are connected in series.
- Within the nephron, the afferent arteriole, glomerular capillaries, efferent arteriole, and peritubular capillaries are all connected in series.
- The RT (total resistance) in a series system is:

$$R_T = R_1 + R_2 + R_3 \ldots$$



$R_T = R_1 + R_2 + R_3$
$= 1 + 2 + 3 = 6$ units of resistance

▲ **Figure 11–5.1** Resistors Connected in Series

- Linking tubes in series creates a high-resistance system.
- Adding a resistance in series always increases the resistance of the system; as in aortic stenosis, coarctation of the aorta. This adds a resistor in series within the systemic system, thus increasing TPR.

5.2 Parallel System

- Tubes connected side by side are connected in parallel.
- The flow can be different when two tubes are in parallel.
- If one concludes that the flow at two points in a vascular system can be different, they are connected in parallel.
- Systemic tissues and organs are connected in parallel.
- The R_T (total resistance) in parallel is:

$$1/R_T = 1/R_1 + 1/R_2 + 1/R_3$$

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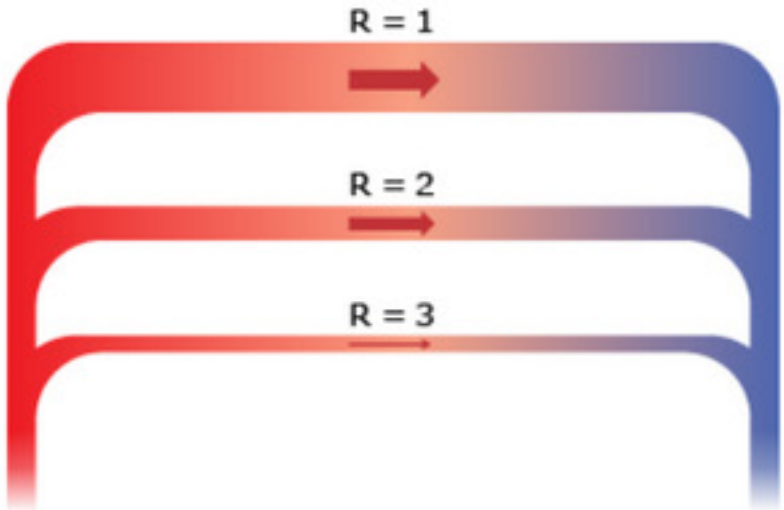
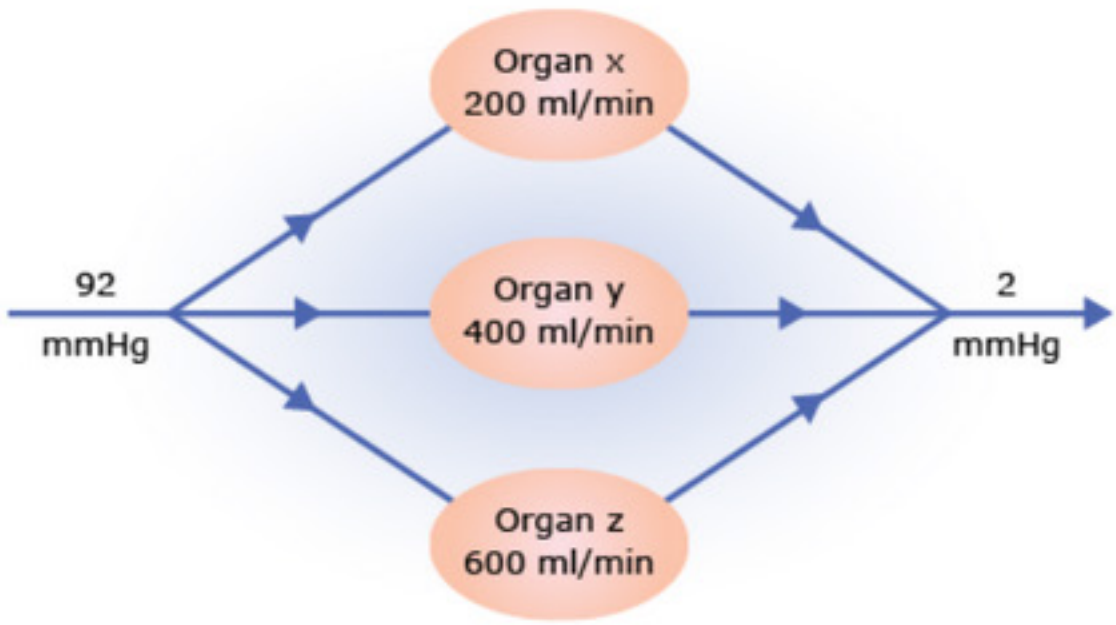


$$
\begin{aligned}
1/R_T &= 1/R_1 + 1/R_2 + 1/R_3 \\
&= 1/1 + 1/2 + 1/3 \\
&= 11/6 \\
R_T &= 6/11
\end{aligned}
$$

▲ **Figure 11–5.2A** Resistors Connected in Parallel

- Linking tubes in parallel creates a low-resistance system.
- Adding a tube in parallel decreases the resistance of the system.
- Obesity adds tubes in parallel within the systemic system, thus decreasing TPR.
- Removing a tube in parallel raises the resistance of the system. Donating a kidney removes tubes in parallel, thus increasing TPR.



▲ **Figure 11–5.2B** Organs Connected in Parallel, a Model of the Systemic Circuit

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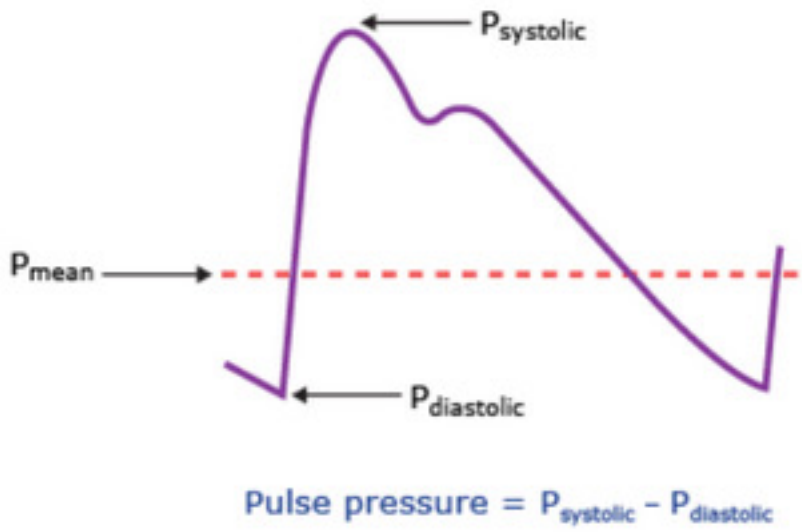
6 The Systemic Arterial System

6.1 Pressure



▲ **Figure 11–6.1A** Systemic Arterial Pulse Pressure

6.1.1 Systolic Blood Pressure (SP)

- Peak pressure in a systemic artery during the cardiac cycle.
- The most important factor determining systolic pressure under most physiological conditions is stroke volume (SV): ↑ SV, ↑ SP; ↓ SV, ↓ SP.
- A secondary factor affecting systolic blood pressure is *aortic compliance*. The aorta contains elastic fibers that stretch expanding the aorta during ejection. This stores volume and energy within the wall and reduces systolic blood pressure. There is then a rebound or vessel recoil during diastole.
- Aging and atherosclerosis reduce aortic compliance, and the reduced stretch during ejection means an increased systolic blood pressure—the greater increase in systolic compared to diastolic blood pressure, with aging, is at least partially due to the reduced aortic compliance.

6.1.2 Diastolic Blood Pressure

- Lowest pressure in a systemic artery during the cardiac cycle.
- The most important factor determining diastolic blood pressure is the resistance of the arterioles (TPR): ↑ TPR, ↑ DP; ↓ TPR, ↓ DP.
- A secondary factor affecting diastolic blood pressure is the recoil of the aorta during ventricular diastole.
- The volume and energy released as the aorta recoils keeps pressure higher as the aorta empties, facilitating delivery of blood to the periphery.

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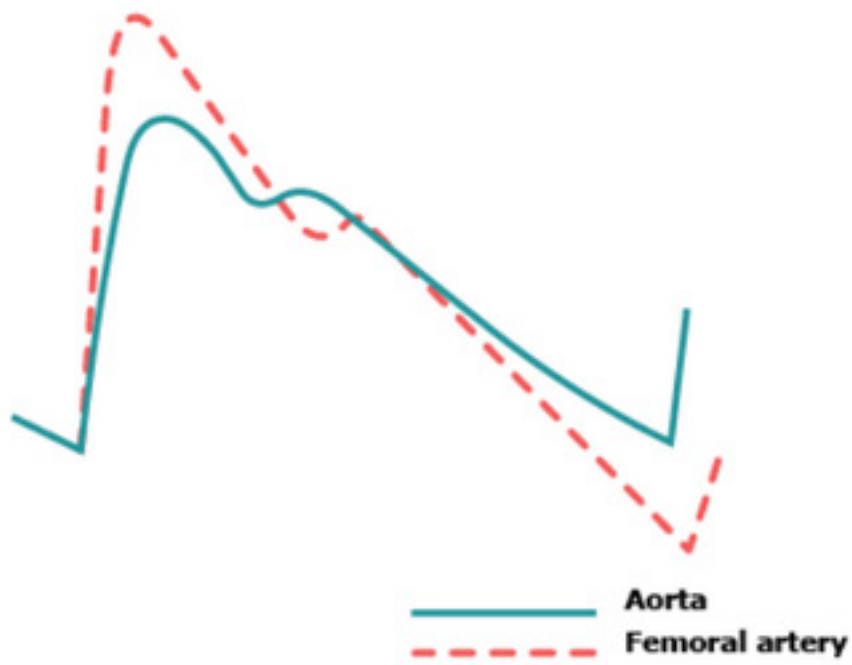
6.1.3 Pulse Pressure

- Pulse pressure is the difference between systolic and diastolic blood pressures.
- The major factor affecting pulse pressure is the compliance of the arterial wall—a compliant artery stretches with ventricular ejection, which reduces systolic blood pressure and recoils in diastole, which keeps diastolic pressure up.
- Compliant arteries have smaller pulse pressure; stiff arteries have larger pulse pressures.
- The aorta is the most compliant artery (most elastic tissue); peripheral arteries are stiffer.



▲ **Figure 11–6.1B** Pressure Pulse of Compliant vs. Stiff Artery

- Heart rate (HR) also affects pulse pressure—as HR ↓, SV ↑, and SP ↑. As HR ↓, the diastolic interval ↑ and DP ↓; therefore, pulse pressure ↑.
- The opposite is true for an increase in heart rate. These changes are independent of venous return.

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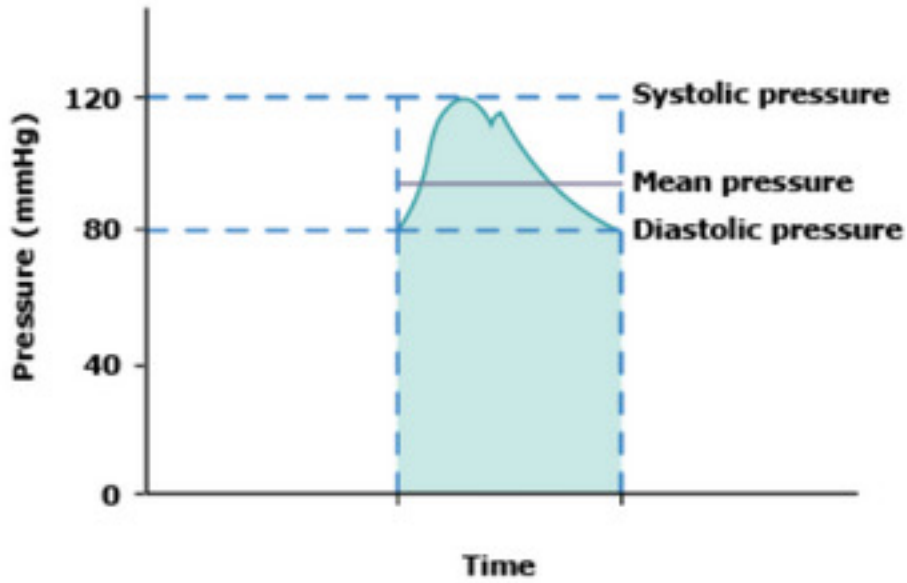
6.1.4 Mean Pressure

- Mean pressure is the average pressure in the artery over the complete cardiac cycle.



▲ **Figure 11–6.1C** Mean Systemic Arterial Pressure

- The shape of the pressure wave form causes mean pressure to be closer to diastolic than it is to systolic pressure.
- Diastolic pressure is a better index of mean pressure than is systolic pressure.
- Mean pressure can be approximated from the following formula:

$$\text{Mean pressure} = \text{diastolic} + 1/3 \text{ pulse pressure}$$

- This formula is most accurate at low heart rates. At high heart rates, it is better estimated as the simple average of systolic and diastolic pressures.
- The factors determining mean pressure are expressed in the derived Poiseuille equation:

$$MAP = CO \times TPR$$

- Cardiac output as stated is the volume circulating in the series system; it does not include the volume stored in the veins or pulmonary circulation.
- TPR is the total resistance of the systemic system but, as stated earlier, it is mainly the resistance of the arterioles.
- As one of the two factors changes, the other factor must change in the opposite direction to maintain a constant mean pressure, as in hemorrhage ↓ CO, therefore ↑ TPR; exercise ↓ TPR, therefore ↑ CO.

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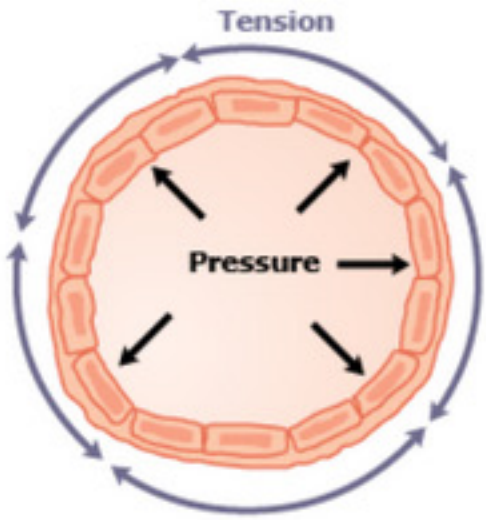
6.2 Aortic Aneurysm and Wall Tension

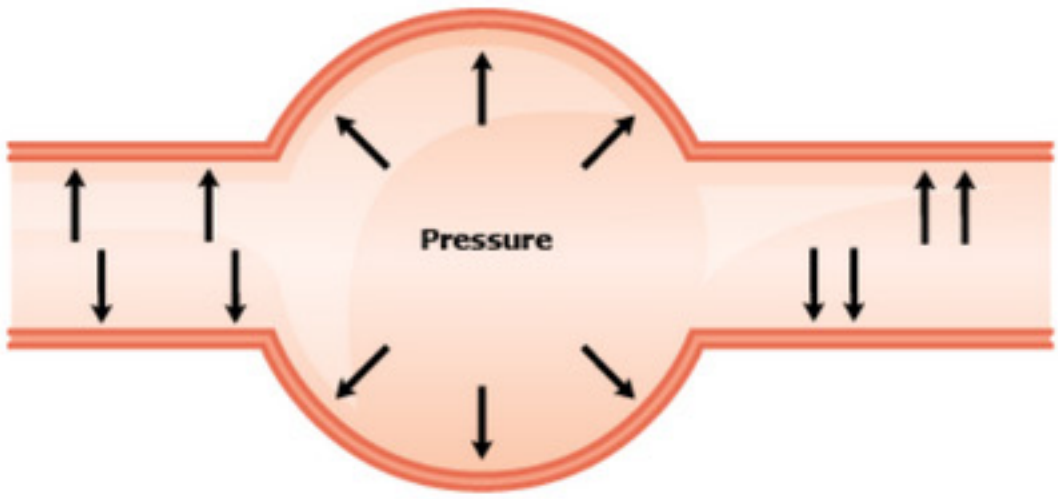
- Wall tension is a stretching force that develops in response to vessel pressure.



$$T \alpha Pr$$

▲ **Figure 11–6.2A** LaPlace Relationship

- The magnitude of the wall tension is the pressure X vessel radius.
- The greatest wall tensions are experienced by the aorta (greatest radius and pressure).
- Peripherally, because arterial radius decreases, wall tension also decreases.
- Aortic aneurysm is an abnormal localized vessel dilation.



▲ **Figure 11–6.2B** Aortic Aneurysm and Wall Tension

- The greater radius of the aneurysm, compared to adjacent regions, means a greater wall tension; this wall tension increases further as the aneurysm enlarges.
- A hypertensive episode also increases an aneurysm's wall tension.
- Aortic aneurysms are most commonly located in the abdominal aorta, and it is in this location that they have the greatest likelihood of rupture.

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6.3 Coarctation of the Aorta

- Congenital narrowing of the aorta is typically located just distal to the origin of the left subclavian artery.
- It sometimes involves the origin of the left subclavian artery, causing a lower blood pressure in the left arm compared to the right.
- High pressure proximal to the stenosis may desensitize baroreceptors, and low pressure distal to the stenosis may activate the renin-AII-aldosterone system.
- Carotid pulse more prominent than femoral pulse, which may be absent.
- Midsystolic murmur best heard between scapulae.

6.4 Peripheral Artery Disease (PAD)

- Generally refers to the consequences of atherosclerotic disease in the arteries of the pelvis or lower limbs.
- It is the degree of vessel narrowing that has the greatest impact on flow (resistance α $1/r^4$).
- The increased resistance can dissipate the arterial pulse (as in the arterioles). Turbulence across a stenosis can further increase resistance to flow and create a bruit.
- Ischemic tissue during exercise induced peripheral vasodilation.
- Dysfunctional atherosclerotic endothelium does not release vasodilators (nitric oxide).
- Claudication often develops with walking.

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7 Venous System

- Contains 70% of the total blood volume and represents the largest blood reservoir (2nd largest pulmonary circuit).
- Blood reservoir (not contributing to cardiac output) easily mobilized only because of the very compliant nature of the venous system.
- Compliance = Δ volume/Δ pressure. It is how easily a vessel is stretched. Easily stretched = very compliant. The opposite = stiff.
- A compliant venous system means that for a small change in venous pressure, there is a large change in venous volume; for example, hemorrhage ↓ venous pressure, ↓↓↓ venous volume and the volume removed from the veins now contributes to CO.
- Passive changes in venous volume due to pressure changes; active changes in volume due to sympathetics.
- Retention of fluid and excessive venous volumes moves the veins from the compliant to stiff range (pressure increases more dramatically), as in low-output heart failure.
- Veins contain one-way valves, and combined with the compression-decompression effect of muscular contraction propels venous return and reduces venous pressure particularly in the dependent regions of the body.
- Varicose veins—dilated, bulbous protrusions beneath the skin of the legs that develop from vessel weakness and increased intraluminal pressures, such as long-term standing, pregnancy, obesity.

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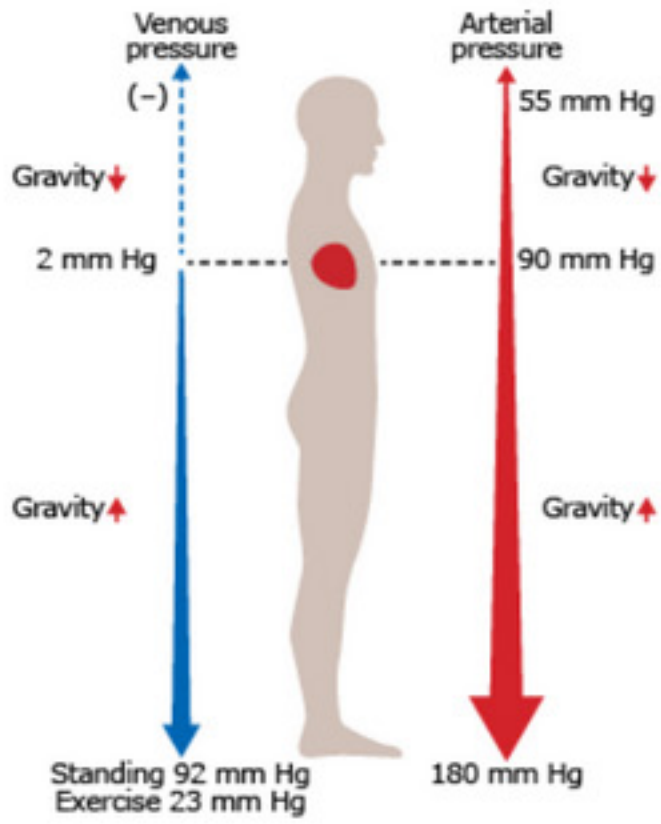
8 Gravity



▲ **Figure 11–8.0** Gravity

- Blood pressure is monitored in an artery at heart level.
- Below heart level, blood pressure increases due to gravity.
- Above heart level, blood pressure decreases.
- Venous system at heart level close to 0 mmHg.
- Below heart level, venous pressure increases, the compliant system dilates; pooling of blood in the dependent veins.
- Venous pressure and volumes reduced due to one-way valves and the muscle pump.
- Supine to standing ↑ dependent venous pressure, ↑ venous volume, ↓ CO, ↓ BP; reduces cerebral perfusion pressure.
- Above heart level, venous pressure decreases to negative values, superficial veins partially collapse, deep veins supported by the surrounding tissue maintain a significant negative pressure, particularly inside the cranium.
- Severing a vein with a negative luminal pressure opens the possibility of introducing air into the systemic venous system, but emboli trapped in the lungs.

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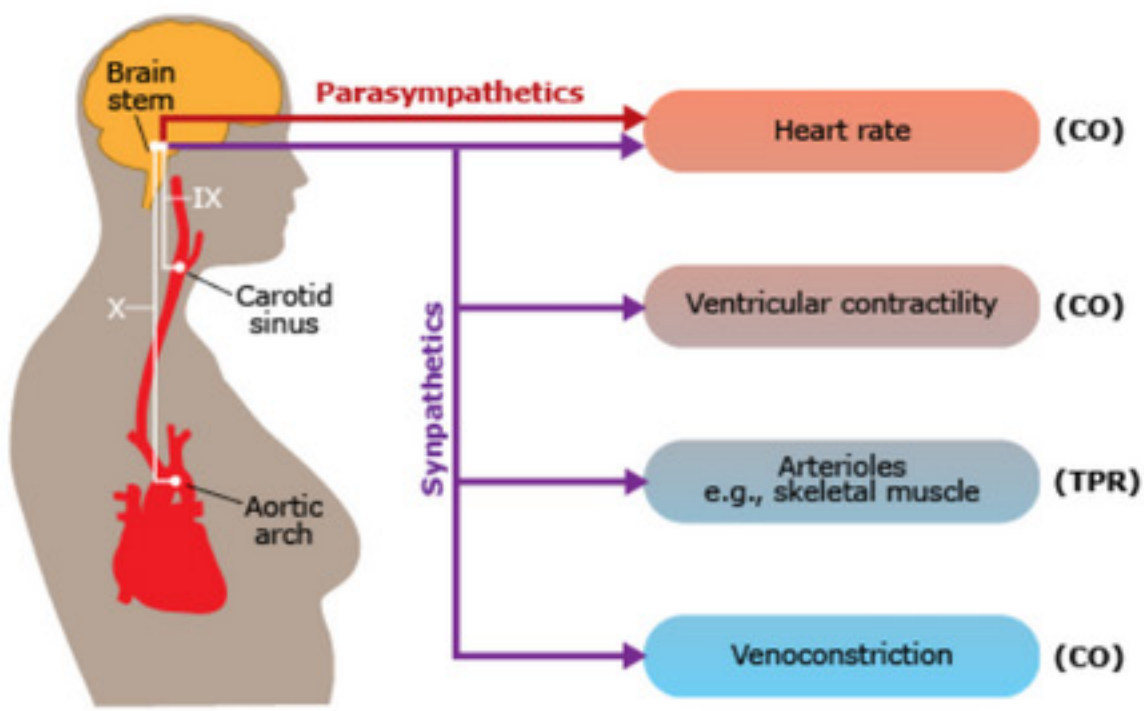
9 Nervous Reflexes in the Control of Blood Pressure

- Acute moment-to-moment regulation of blood pressure is via the *baroreceptors*. They quickly respond to an insult and bring blood pressure back toward normal, but compensation is usually not complete.
- Chronic regulation of blood pressure involves volume control mainly via the renin-AII-aldosterone system; this system is slow to respond to an insult, but compensation is generally complete.

Note: Any decrease in blood pressure activates this system, and volume retention continues until blood pressure returns to normal. ADH also participates via high-pressure and low-pressure baroreceptors.

- The control of blood pressure involves altering the two factors that determine MAP.

$$MAP = CO \times TPR$$



▲ **Figure 11–9.0** Nervous Reflexes in the Control of Blood Pressure

- Receptors are located in the carotid sinuses (afferents via IX nerve) and the aortic arch (afferents via X nerve).
- Carotid sinuses are slightly dilated areas at the origin of the internal carotid arteries.
- Receptors monitor stretch of the vessel wall as an index of blood pressure.
- The carotid sinus receptors are more sensitive than those of the aortic arch.
- The brain stem interprets the afferent activity. ↑ afferent activity → signals hypertension, ↓ afferent activity → signals hypotension.

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- Output via the parasympathetic and sympathetic system, which is modified to bring blood pressure back toward normal.
- Sensitivity of the system known to decrease in hypertension and low-output heart failure.

9.1 Reflex Response

Blood Pressure	Afferent Frequency	Sympathetic Response	Parasympathetic Response
↓	↓	↑	↓
↑	↑	↓	↑

9.2 Changes in Circulating Volume

Volume (CO)	Afferent Frequency	Sympathetic Response	Parasympathetic Response	Blood Pressure	Heart Rate
↓	↓	↑	↓	92 ↓ <<92; <92 reflex	↑
↑	↑	↓	↑	>>92 reflex >92; 92 ↑	↓

↓volume = hemorrhage, dehydration, venodilation, diarrhea, supine to standing
↑volume = over-transfusion, fluid ingestion, venoconstriction, weightless environment

9.3 Special Maneuvers

Maneuver	Afferent Frequency	Sympathetic Response	Parasympathetic Response	Blood Pressure	Heart Rate
Carotid Massage	↑	↓	↑	↓	↓
Carotid Stenosis (before sinus)	↓	↑	↓	↑	↑
Block Afferent Activity	↓	↑	↓	↑	↑

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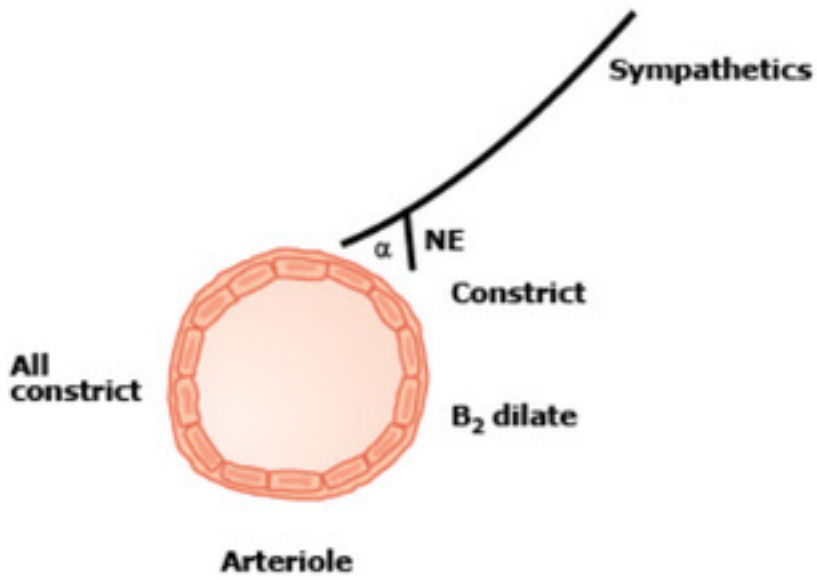
1 Extrinsic Regulation of Systemic Arterioles



▲ **Figure 12–1.0** Extrinsic Regulation of Systemic Arterioles

- Sympathetic vasoconstrictors are distributed to the arterioles and arteries of all systemic tissues but in a non-uniform manner; as such, the response varies among the tissues, from no significant response in the cerebral vasculature to a maximum response in resting skeletal muscle and the cutaneous vessels.
- Sympathetic vasoconstrictors releasing NE and acting on α receptors causing a vasoconstriction represents the main extrinsic regulation of the arterioles.
- When present, β_2 receptors cause a vasodilation when acted upon by circulating epinephrine from the adrenal medulla.

Note: Norepinephrine always causes a vasoconstriction; low doses of epinephrine cause a vasodilation, but high doses cause a vasoconstriction.

- Angiotensin II has a constrictor effect and plays a significant role in regulating TPR.
- Parasympathetics have little if any vasodilatory effect on systemic arterioles—the exception is the penis.
- Sympathetic vasodilator fibers innervate skeletal muscle arterioles and participate in the vaso-vagal syncope—vagal fibers slow heart rate, and sympathetics dilate skeletal muscle arterioles.

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2 Autoregulation in Systemic Tissues

- In some systemic tissues, changes in perfusion pressure or metabolism induce changes in vascular resistance to maintain a balance between oxygen supply verses tissue demands.
- This intrinsic phenomenon is referred to as *autoregulation*.
- The tissue induces changes in resistance to control the flow; it is flow, not resistance, that is regulated.
- Autoregulation is independent of circulating substances and nervous reflexes (carotid sinus).
- Circulating effects of norepinephrine released from sympathetic nerve endings and epinephrine from the adrenal medulla are independent of autoregulatory control.
- Tissues exhibiting strong autoregulation include: the cerebral circulation, coronary circulation, and skeletal muscle during exercise.
- The kidneys also exhibit strong autoregulation under normal physiological conditions.

2.1 Myogenic Hypothesis

- Increased perfusion pressure stretches the vascular smooth muscle surrounding the arterioles.
- The response to stretch is a greater degree of constriction. This is an inherent property of vascular and intestinal smooth muscle cells.
- The mechanism may involve activation of membrane-bound calcium channels.

2.2 Metabolic Hypothesis

- In an autoregulating tissue, metabolic processes release *vasodilatory* substances that relax the smooth muscle cells of the arteriolar wall.
- Metabolic response: ↑ metabolism ↑ vasodilatory metabolites ↓ arteriolar resistance, ↑ blood flow—blood flow is proportional to tissue metabolism.
- Blood pressure response: ↑ BP ↑ blood flow, ↑ washout of metabolites, ↑ arteriolar resistance, ↓ blood flow toward original level—blood flow is independent of perfusion pressure.
- In addition, endothelial-derived relaxing factors contribute to the regulation of blood flow.

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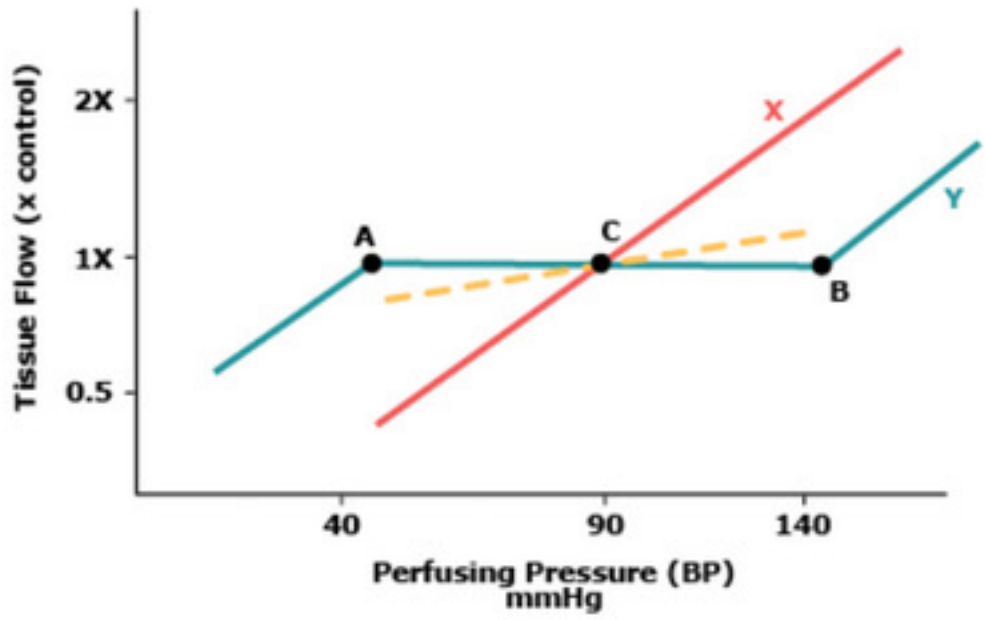
- An increase in flow, and the consequent increased shear stress on the endothelial cells of small arteries, release NO, which dilates the smooth muscle locally—this decreased resistance of small arteries upstream from the arterioles contributes to an autoregulatory increase in flow.



▲ **Figure 12–2.2** Autoregulation

- **Line X (red):** No autoregulation: pressure-dependent flow.
- **Line Y (green):** Perfect autoregulation between point A and B, which is also the autoregulatory range of the tissue.
- **Dashed line:** Some degree of autoregulation; the flatter the line, the better the autoregulation.
- **C → B:** Vasoconstriction to maintain flow constant. Point B represents maximum constriction of the arterioles.
- **C → A:** Dilation to maintain flow constant. Point A represents maximum dilation of the arterioles.

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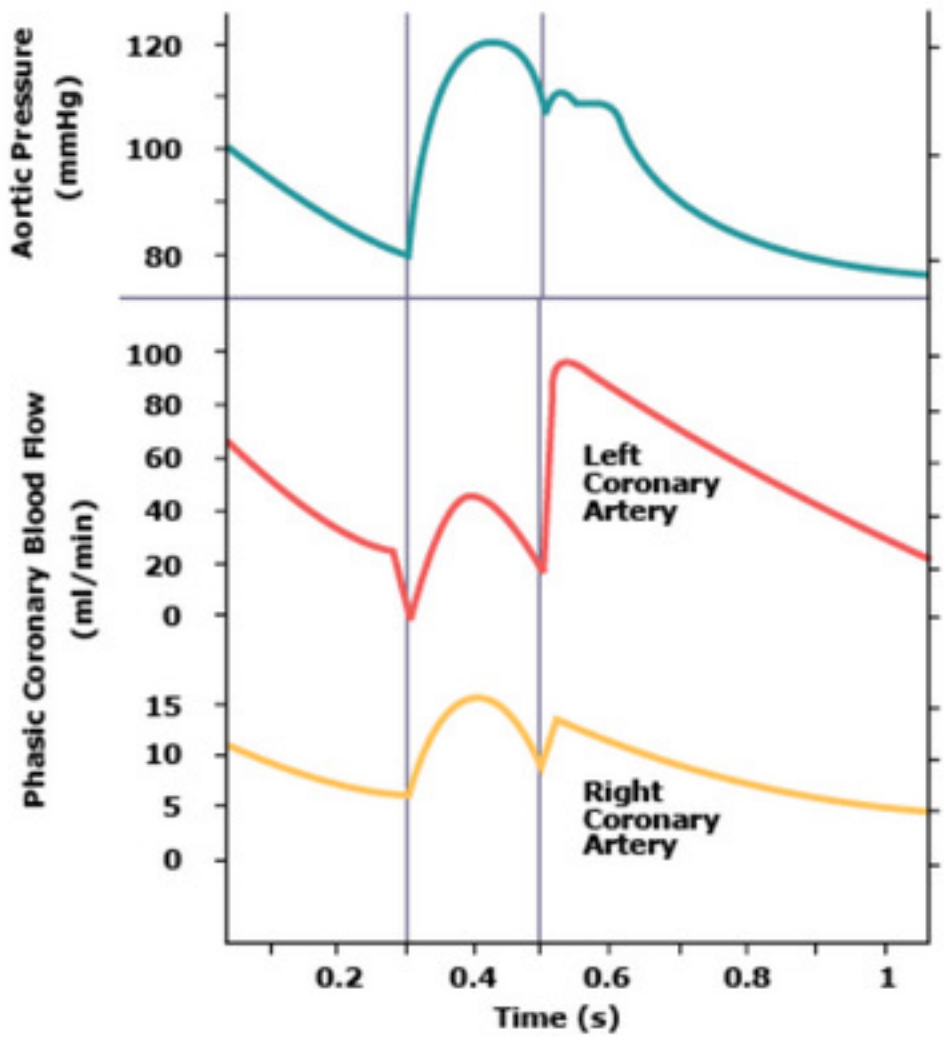
3 The Coronary Circulation

- Coronary arteries course over the surface of the myocardium and at right angles give off branches that penetrate the myocardium. Most of the blood returns to the right atrium through the coronary sinus.



▲ **Figure 12–3.0** Coronary Circulation

3.1 Left Coronary Flow (Left Ventricular Myocardium)

- During ventricular systole, the intramyocardial vessels experience a severe mechanical compression that limits tissue perfusion.
- Compression forces increase from the subepicardium to the subendocardium.
- The compression at the beginning of systole causes a retrograde flow in the epicardial vessels and then a brief high antegrade flow at the beginning of diastole when the vessels refill.
- Most of the flow to the left ventricle is a diastolic phenomenon, the magnitude of which depends on autoregulatory control of the coronary arterioles via tissue metabolites and endothelial-derived relaxing factors, mainly NO.
- The coronary circulation is unique in that oxygen extraction is almost maximal even under resting conditions, so flow must be proportional to myocardial metabolism.
- ↑ BP, ↑ pressure work, ↑ coronary flow.

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- ↑ CO (exercise), ↑ volume work, ↑ coronary flow.
- Pressure work is more demanding than volume work of the heart.
- The coronary arteries contain α-adrenergic and β-adrenergic receptors; but, in the absence of endothelial dysfunction, their activation has no significant influence on coronary blood flow.

3.2 Right Coronary Flow (Right Ventricular Myocardium)

- Flow pattern is similar to that of the left coronary, except there is less mechanical compression.
- More of the total flow occurs during systole, and dilation of the coronary resistance vessels can increase systolic flow.

3.3 Coronary Artery Disease

- In coronary artery disease, the atherosclerotic plaques develop in the epicardial conductance vessels. The intramyocardial resistance vessels are generally plaque-free and are able to dilate in response to any increase in metabolic demands of the tissue.
- The normal heart has essentially no collateral circulation.
- If a coronary artery slowly narrows over time, collaterals develop, protecting portions of the muscle, particularly the subepicardial region following coronary occlusion, and, in some cases, this limits the infarction to the subendocardium.
- The consequences of coronary artery disease depend on the degree of fixed stenosis and endothelial dysfunction.
- < 50–60% narrowing of an epicardial conductance vessel does not compromise the maximal potential blood flow with the increased metabolic demands of exercise.
- > 50–60%, < 80–90% narrowing—Stable Angina—narrowing provides adequate blood flow under resting conditions, but the coronary reserve is compromised.
- Angina at fixed exercise workloads with temporary ST segment depression—no permanent myocardial damage.
- 80–90% narrowing—Unstable Angina—coronary flow can be compromised at rest or with very light exercise.
- Resting angina—no enzymatic evidence of tissue damage, but at high risk for myocardial infarction.
- Variant Angina—Coronary artery spasm, even in the absence of coronary artery disease. Occurs mainly at rest and typically produces complete occlusion of the epicardial vessel, ST segment elevation.
- Silent Angina—Asymptomatic, EKG identification of ischemic tissue.

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3.4 Myocardial Ischemia

- An imbalance between oxygen supply versus tissue demands.
- In addition to coronary artery disease, the following accentuate or promote the development of myocardial ischemia: aortic stenosis, aortic regurgitation, hypertension, hypotension, and elevated heart rates.
- Endothelial dysfunction can unmask sympathetic vasoconstrictors effects.
- Consequences:
  - ↓ systolic contraction—systolic dysfunction
  - ↓ diastolic relaxation—diastolic dysfunction
  - ↓ compliance of the ventricle with ↑ diastolic pressure transmitted back to the pulmonary circulation with possible pulmonary congestion and dyspnea
  - ↓ Na^+/K^+- ATPase pump, depolarization and fast fiber → slow fiber, K^+: ICF → ECF, local hyperkalemia
  - ↑ ICF water and cell swelling due to accumulation of intracellular metabolites
  - ↑ ICF Na
  - ↑ ISF edema

3.5 Treatment

- Chronic coronary artery disease creates an imbalance between oxygen supply versus myocardial demand. Treatments are aimed at maintaining this balance and focus on reducing the oxygen demands of the myocardium.
- β1 adrenergic antagonists: Reduce myocardial oxygen demands by decreasing heart rate and contractility.
- Calcium channel blockers: Decrease myocyte and smooth muscle contraction (peripheral vasodilation and decrease TPR).
- Nitrates: Principal effect is by dilating peripheral capacitance veins, but also a dilation of the coronary vasculature.

Note: Decreasing TPR to decrease the pressure work of the heart (afterload) and/or dilating the veins to decrease the volume work of the heart reduces the overall oxygen demands of the myocardium

3.6 Acute Coronary Syndromes and Infarction

- Most result from disruption of an atherosclerotic plaque along with platelet aggregation and the formation of an intracoronary thrombus.
- A dysfunctional endothelium increases the chances of thrombus formation.
- Partial occlusion thrombus related to non-ST-elevation myocardial infarction (NSTEMI) or an unstable angina (enzymatic evidence of tissue infarction absent).
- Complete occlusion results in a more severe ischemia and necrosis and an ST-elevation myocardial infarction (STEMI).

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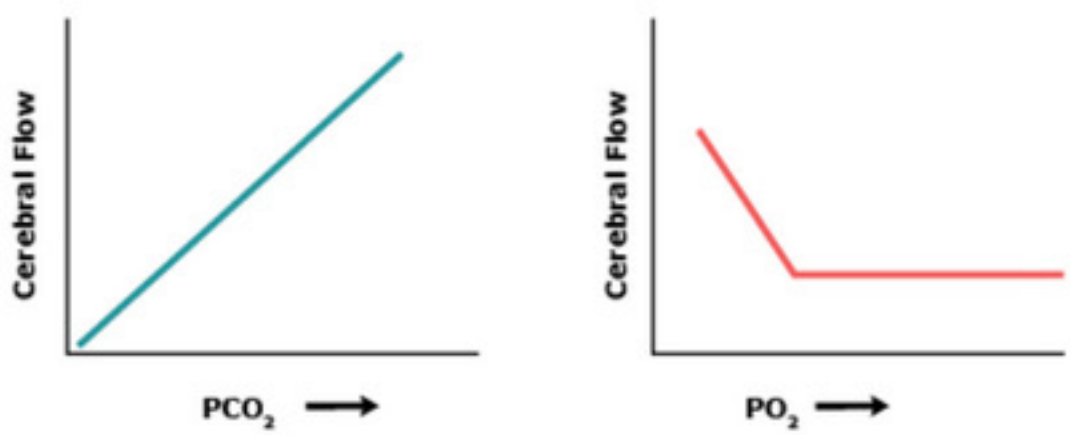
4 The Cerebral Circulation

- Under normal conditions, cerebral blood flow is proportional to systemic arterial CO_2—the main factor controlling flow.
- Hyperventilation ↓ arterial CO_2—constricts cerebral vasculature.
- Hypoventilation ↑ arterial CO_2—dilates cerebral vasculature.
- The CO_2 diffuses across the blood-brain barrier to the vascular smooth muscle. H^+ is the final effector.
- Due to the fact that H^+ does not easily cross the blood-brain barrier, arterial pH does not significantly affect cerebral blood flow, but a ↓ CSF pH dilates.
- Arterial PO_2 has no significant effect on cerebral blood flow as long as it is in the normal range or above normal.
- A decrease in arterial PO_2 dilates regardless of the PCO_2. Hyperventilation in the presence of a low arterial PO_2 dilates.
- Since the cerebral circulation resides within a rigid structure, a rise in CSF pressure mechanically compresses the vessels compromising cerebral blood flow. Cushing reflex is the compensation. Independent of the carotid sinus there is a severe peripheral vasoconstriction that raises blood pressure to overcome the mechanical compression. Presumably, the carotid sinus does respond by decreasing heart rate (Cushing reflex ↑ BP ↓ HR).



▲ **Figure 12–4.0** Regulation of Cerebral Blood Flow

Note: The coronary and cerebral vasculatures are innervated by sympathetic neurons. They play no role regulating cerebral blood flow under normal conditions, and their constrictive effects on the coronary circulation are normally masked by the contractility changes of the myocardium, which induce a vasodilation.

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5 The Cutaneous Circulation

- Primary function is to maintain a constant body temperature.
- Main control is via sympathetic adrenergic nerves (NE on α-adrenergic receptors).
- Sympathetic innervation of: arterioles, A–V anastomoses and large venous plexus.
- Sweat glands innervated by sympathetic cholinergics.
- Warm environment: skin dilates (↓ sympathetic stimulation).
- Cold environment: skin constricts (↑ sympathetic stimulation).
- Local responses to cold and heat on skin surface; therefore some local control.
- Fever: There is no loss in the ability to regulate body temperature; it is simply regulated at a higher set point.
- Development of a fever: Skin constricts, body temperature ↑.
- Fever *breaks*: Skin dilates and sweating, body temperature ↓.

6 Skeletal Muscle

6.1 Resting Muscle (Extrinsic regulation)

- Main control is via sympathetic adrenergic neurons.
- β_2: dilates via circulating epinephrine.
- AII: vasoconstriction.
- Arterioles have a high degree of basal tone and sensitive to the carotid sinus reflex:

  ↑ BP ↓ sympathetics—dilation

  ↓ BP ↑ sympathetics—constriction
- A major regulator of TPR because of the large mass of tissue.

6.2 Exercising Muscle (Autoregulation)

- Main control is via vasodilatory metabolites.
- Sympathetic adrenergic nerves have only a small influence on flow.
- β_2: dilates via circulating epinephrine.
- Phasic contractions of the muscle facilitate flow and venous return.

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7 Gastrointestinal

- Main control is via sympathetic adrenergics.
- Autoregulatory flow increase following a meal.
- Hepatic circulation 75% hepatic portal, 25% hepatic artery.
- Hepatic portal system does not autoregulate.
- Elevation of systemic venous pressure causes filtration of fluid from the liver to the peritoneal cavity—ascites.
- Cirrhosis increases hepatic vascular resistance and pressure in the portal venous circulation, increases capillary pressure in the splanchnic capillaries, and increased filtration—ascites.

8 Renal Circulation

- Under normal conditions, the kidney exhibits strong autoregulation.
- With severe hypotension, the kidney constricts, and renal function is lost.
- Kidney receives 20–25% of cardiac output. In terms of nutrient and oxygen delivery, the kidney is greatly over-perfused.

Note: If a systemic tissue is over-perfused, the venous PO_2 is high; if a systemic tissue is under-perfused, the venous PO_2 is low.

α-agonist—vasoconstricts and promotes under-perfusion;
α-antagonist—vasodilates and promotes over-perfusion.

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9 Fetal Circulation

- Fetal lungs are in a compressed state with very high vascular resistance.
- Placental circulation is responsible for gas exchange.
- Umbilical circuit is a very large parallel circuit within the systemic system. It receives about 55% of the cardiac output from the descending aorta (Hb sat 58%, low PO_2).
- Systemic system is a very *low*-resistance, *low*-pressure system.
- Umbilical veins have the highest PO_2 of the fetal circulation.
- Some umbilical venous blood is delivered to the liver, and the remainder enters the inferior vena cava by the ductus venosus.
- Umbilical venous blood tends to maintain its own stream and is shunted by the crista dividens through the foramen ovale into the left atrium, left ventricle, and is pumped into the ascending aorta, where it perfuses the upper body region of the fetus.
- The lower-PO_2 blood entering the right atrium from the vena cava passes into the right ventricle and is pumped into the pulmonary artery. Very little of that blood passes through the high-resistance pulmonary circuit.
- Pulmonary system is a *high-resistance, high-pressure* system.
- Pulmonary flow is shunted by the ductus arteriosus to the descending aorta to perfuse the lower body region and the umbilical circuit.
- Following delivery, the umbilical circuit is lost. This raises TPR and systemic arterial pressure
- Inflation of the newborn's lungs decreases pulmonary resistance, initiating pulmonary blood flow through the lungs.
- Decreasing right ventricular afterload decreases right atrial pressure. The high flow through the pulmonary circuit raises left atrial pressure. This combination closes the foramen ovale.
- The increased TPR raises systemic arterial pressure and the lung inflation lowers pulmonary resistance and pressures. This reverses the flow through the ductus.
- Before delivery, low-PO_2 blood flows from the pulmonary artery to the aorta.
- After delivery, high-PO_2 blood flows from the aorta to the pulmonary artery.
- The high PO_2 of the blood passing through the ductus causes a constriction to slowly close the ductus to blood flow.

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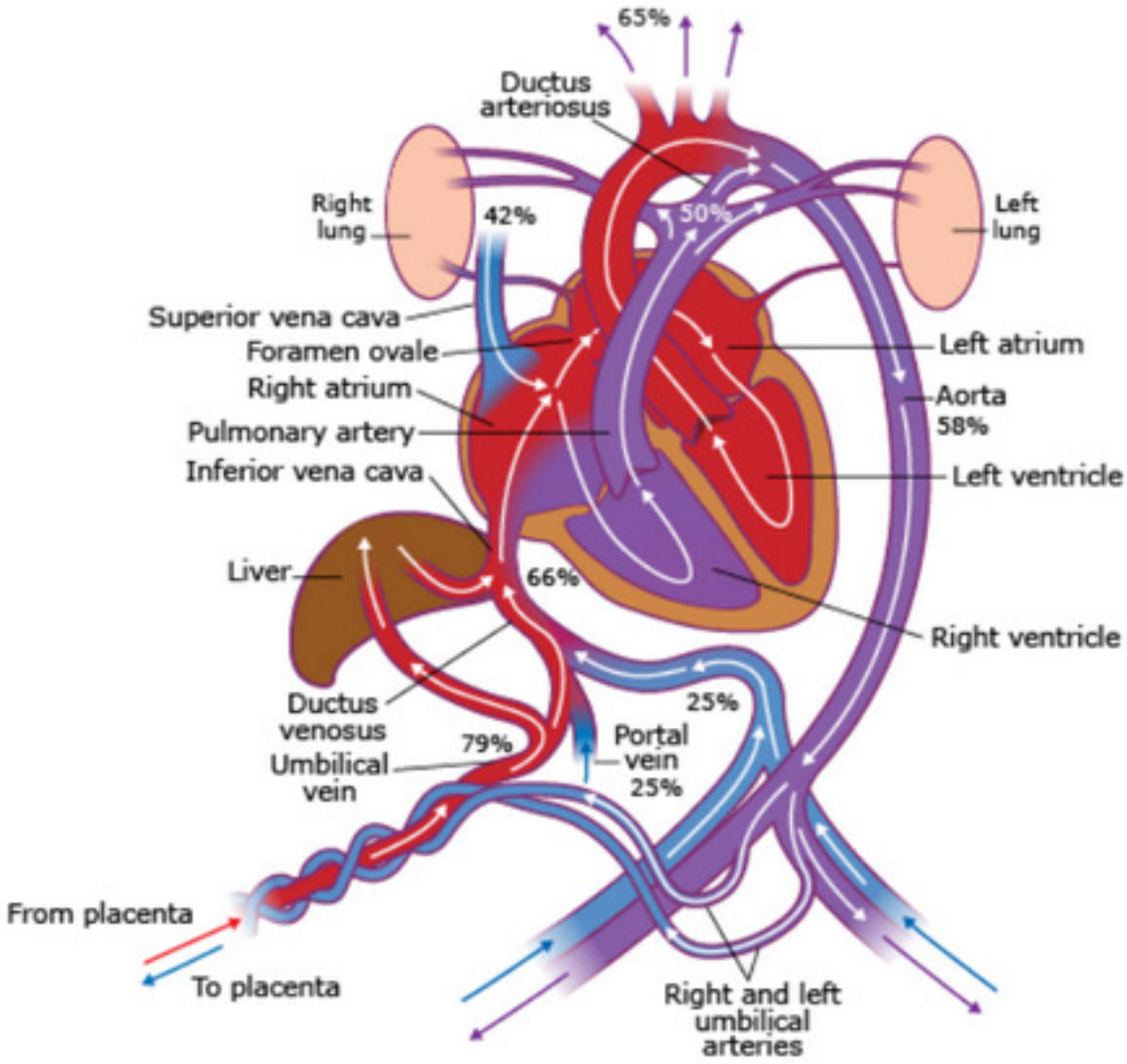

▲ **Figure 12–9.0** Fetal Circulation

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Unit 5

Cardiovascular Integration and Heart Disease

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CHAPTER 13 Cardiac Output: Integration of Cardiac and Vascular Factors

1 Introduction

The cardiovascular system is a closed circuit with the pulmonary and systemic circuits in series. Flow at any point in a series system must be the same. Thus, *venous return* and *cardiac output* are terms for the flow in this series system.

1.1 Function of the Heart

The heart's function is to pump the blood returned to it. If it does not, then by definition it is heart failure. Blood will then pool in the venous system, and venous pressure increases.

- Cardiac function curves describe the heart's pumping ability.
- Vascular function curves (venous return curves) describe the peripheral factors affecting the flow through the circuit.
- The cardiovascular system operates at the intersection of the two curves, which is the equilibrium point for the system.

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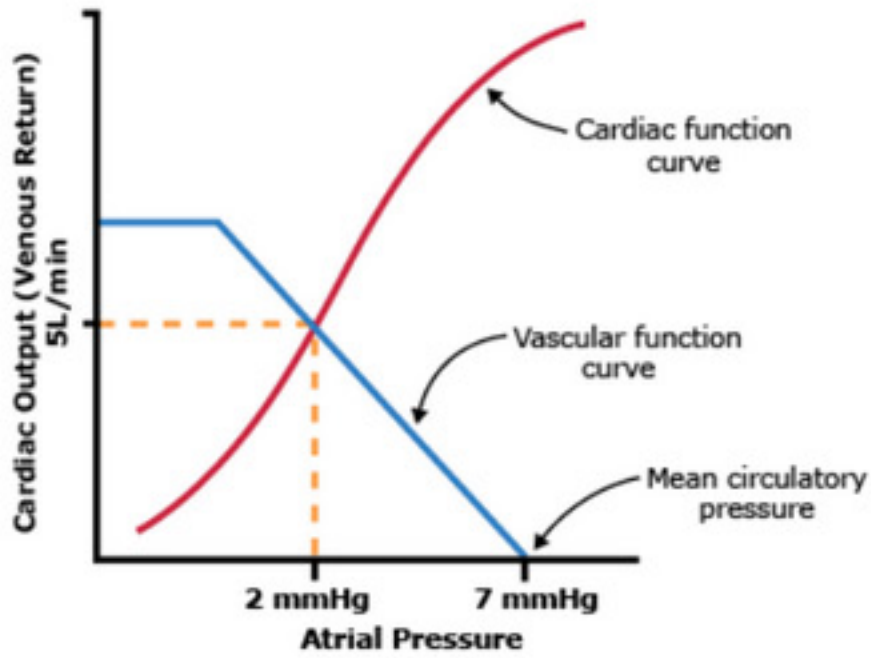
2 Graphical Displays

2.1 Reference Graph

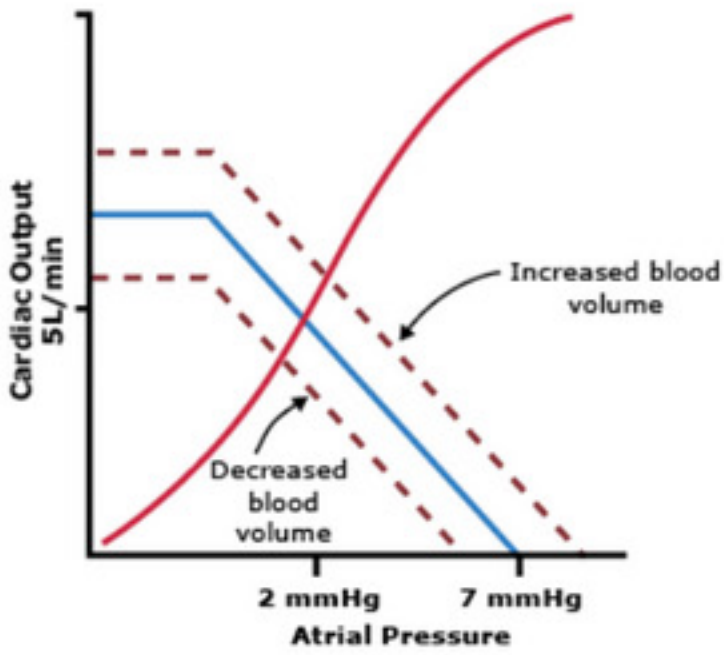
- The *Y*-axis is an index of ventricular function. The best indices are a measure of the work performed by the ventricle: cardiac output × blood pressure, stroke work, stroke power. Cardiac output is a measure of the nutrient flow to the tissues.
- The *X*-axis is an index of the filling of the ventricle or preload; end-diastolic volume or pressure, atrial pressure, venous pressure.
- Mean circulatory pressure = mean systemic pressure. MSP is the equilibrium pressure in the cardiovascular system with the heart stopped. It depends mainly on the total blood volume (BV) of the circuit. A normal value is about 7 mmHg. ↑ BV = ↑ MSP, ↓ BV = ↓ MSP. MSP also increases with venoconstriction.



▲ **Figure 13–2.1** Cardiac Function and Vascular Function Curves: A Reference Grap

- Cardiac function curve = constant contractility; ↑ contractility = left shift, steeper slope, ↓ contractility = right shift, flatter curve.

2.2 Changes in Vascular Volume



▲ **Figure 13–2.2** Cardiac Function and Vascular Function Curves: Effect of Blood Volume

- ↑ blood volume or venoconstriction = ↑ mean systemic pressure, no change in slope.
- ↓ blood volume or venodilation = ↓ mean systemic pressure, no change in slope.

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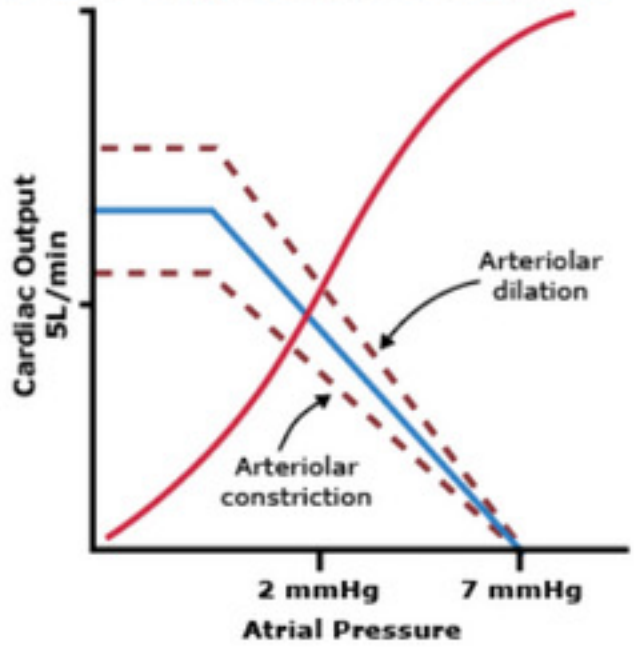
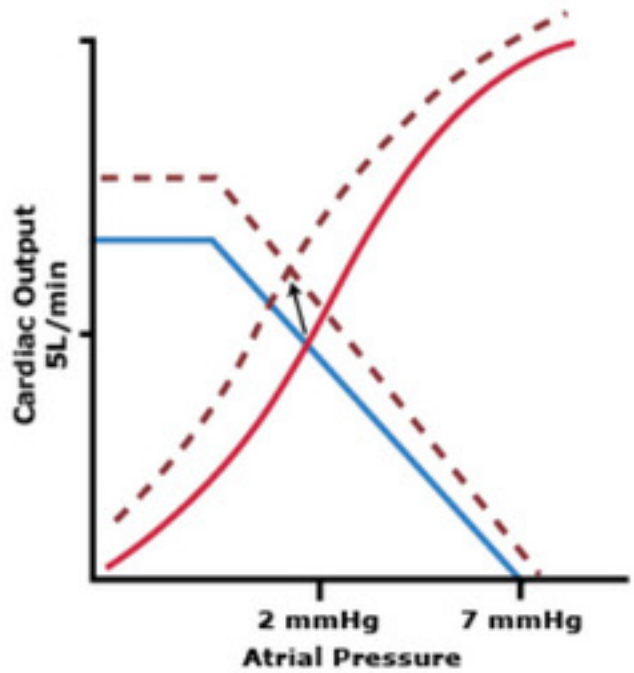
2.3 Changes in Peripheral Resistance



▲ **Figure 13–2.3** Cardiac Function and Vascular Function Curves: Effect of Arteriolar Resistance

- Vasodilation of arterioles = increased venous return; no change in mean systemic pressure.
- Vasoconstriction of arterioles = decreased venous return; no change in mean arterial pressure.

2.4 Exercise



▲ **Figure 13–2.4** Cardiac Function and Vascular Function Curves: Effect of Exercise

- Dilation of the arterioles combined with venoconstriction increases the slope of the vascular function curve, as well as an ↑ MSP.
- ↑ contractility shifts the cardiac function curve to the left.
- Overall: ↑ cardiac output at a slightly lower right atrial pressure.

  Note: Heart rate is not considered in the variables. An increase in heart rate during exercise maintains the elevated cardiac output at a reduced right atrial pressure.

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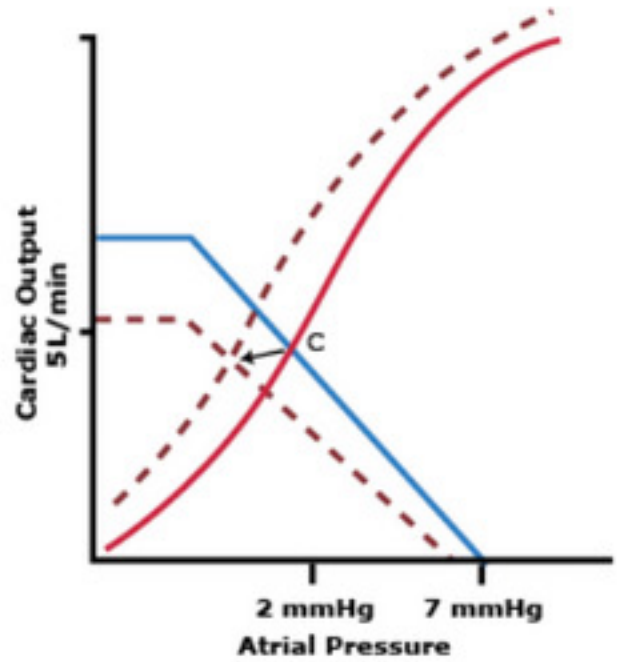
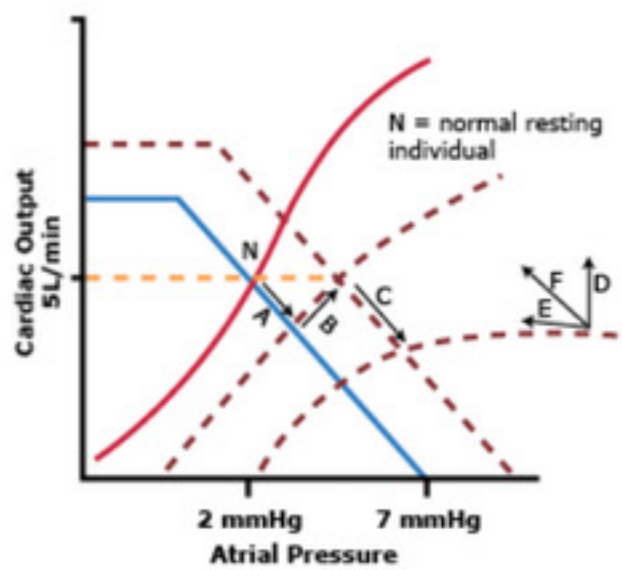
2.5 Hemorrhage



▲ **Figure 13–2.5** Cardiac Function and Vascular Function Curves: Effect of Hemorrhage

- ↓ blood volume = ↓ mean systemic pressure.
- Vasoconstriction = ↓ slope of vascular function curve.
- ↑ contractility = cardiac function curve shifted to the left.
- Overall: ↓ blood volume, vasoconstriction, ↑ contractility, ↓ cardiac output.
- The vasoconstriction (↑ TPR) compensates to a great extent for the ↓ CO, therefore, depending on the magnitude of the blood loss, little change in blood pressure.

2.6 Low-Output Heart Failure



▲ **Figure 13–2.6** Cardiac Function and Vascular Function Curves: Effect of Heart Failure

- Vector A = loss of contractility.
- ↓ performance of the ventricle, ↓ cardiac output, ↓ ejection fraction, ↑ preload.
- ↓ perfusion pressure to the kidney, ↑ renin, ↑ AII, ↑ aldosterone and retention of fluid.

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- Vector B = retention of fluid shifts vascular function curve to the right, cardiac output returns to normal.
- Compensated low-output failure, fluid retention terminated.
- Vector C = further loss of contractility, ↑ activity renin-AII-aldosterone system and further retention of fluid.
- Patient moves onto the flat part of the cardiac function curve, but no matter how much fluid is retained, CO remains below normal; decompensated state with pulmonary congestion.

2.6.1 Treatment

- Vector D = consequences of giving digitalis: ↑ contractility and a shift of cardiac function curve to the left, work of the heart increased to return cardiac output toward normal. Treatment with digitalis has not been shown to decrease mortality and is no longer a chronic therapy. It is most often used with acute decompensation.
- Vector E = diuretic therapy: Because the patient is on the flat part of the cardiac function curve, a decreased preload that reduces pulmonary congestion does not cause a significant reduction in cardiac output. In fact, there may be a slight increase in cardiac output due in part to a Laplace effect. A reduced radius of curvature means that the same ventricular wall tension develops a greater chamber pressure, increasing stroke volume. Loop diuretics are most commonly used in treatment of heart failure. But again, no mortality benefits are seen with the use of diuretics.
- Vector F = ACE inhibitor therapy: The vector on the graph is the same as a combined digitalis-diuretic therapy. Inhibition of aldosterone provides the sodium and water diuresis. Inhibiting the formation of AII increases cardiac output, not by increasing the work of the heart as with digitalis, but by a vasodilatory reduction in blood pressure. Work = BP × CO. By reducing blood pressure CO can be elevated with the decreased work capacity of the failing heart. By keeping blood pressure down, mortality is also reduced.
- Combination therapy of ACE inhibitors, β antagonists and vasodilators demonstrates significant mortality reductions and is becoming the new cornerstone of therapy.

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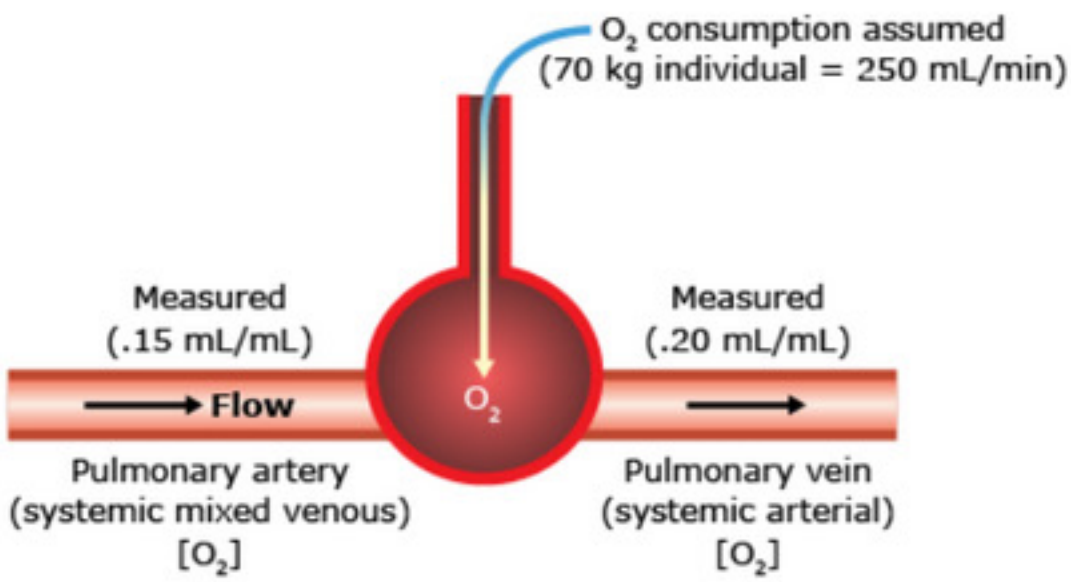
3 Measurement of Cardiac Output

Three clinical procedures are often used to measure cardiac output:

1. **Doppler Echocardiographic**—A noninvasive method that estimates cardiac output as aortic velocity × cross-sectional area.
2. **Thermodilution**—Cold saline injected into the right atrium and blood temperature monitored in the pulmonary artery. Cardiac output is calculated from the slope in the decay of temperature as the saline passes. Most accurate at normal and elevated cardiac outputs.
3. **Fick Principle**—Based on the following relationship:

$$\text{Organ blood flow} = \frac{\text{rate of uptake of a substance}}{\text{AV concentration difference}}$$

When applied to the lung, the rate of uptake is oxygen, and the flow is cardiac output.



▲ **Figure 13–3.0** Cardiac Output Determination: Fick Principle

$$\text{Cardiac output} = \frac{\text{Body oxygen consumption}}{\text{Pul venous } [O_2] - \text{Pul arterial } [O_2]}$$

$$= \frac{250 \text{ mL/min}}{0.20 \text{ mL/mL} - 0.15 \text{ mL/mL}}$$

$$= 5{,}000 \text{ mL/min} = 5 \text{ L/min}$$

$[O_2]$ concentration = 15 volume%
= 15 volumes (mL) / 100 volumes (mL)
= 0.15 mL/mL

Most accurate at low cardiac outputs. Accuracy decreases as cardiac output increases.

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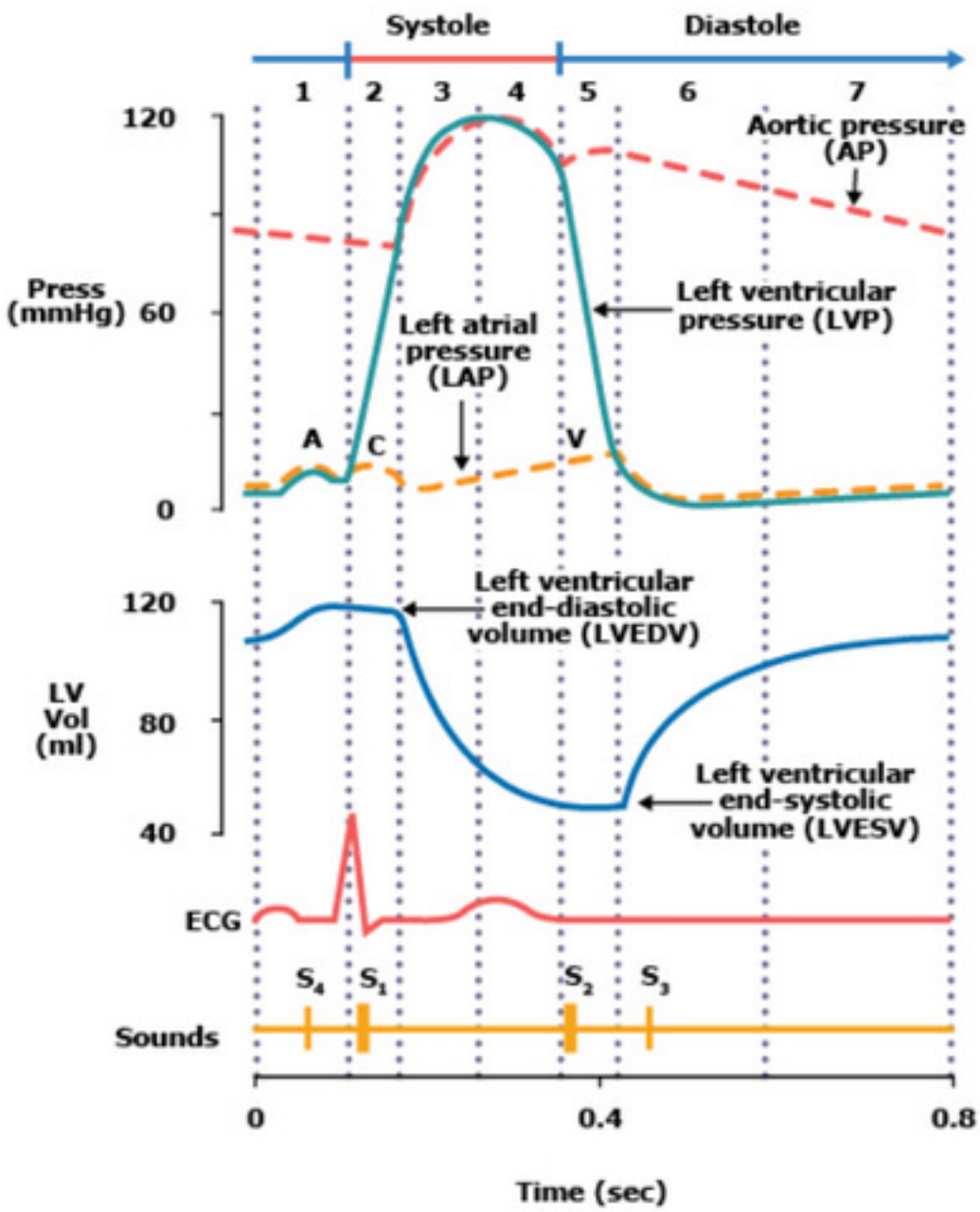
1 The Complete Left-Sided Cycle



▲ **Figure 14–1.0** The Cardiac Cycle

The cardiac cycle for the left heart can be divided into a number of phases and events:

- Atrial contraction (1)
- Closure of mitral valve
  Isovolumetric contraction phase (2)
- Opening of aortic valve
  Ejection phase—rapid ejection (3), reduced ejection (4)
- Closure of aortic valve
  Isovolumetric relaxation phase (5)
- Opening of mitral valve
- Filling phase—rapid filling (6), reduced filling (diastasis) (7)
  - The opening and closing of the valves is due to pressure differences across the valve
  - Right side similar to the left, except the pressures are only ¼ that of the left heart
  - Ventricular systole much shorter than diastole at resting heart rates

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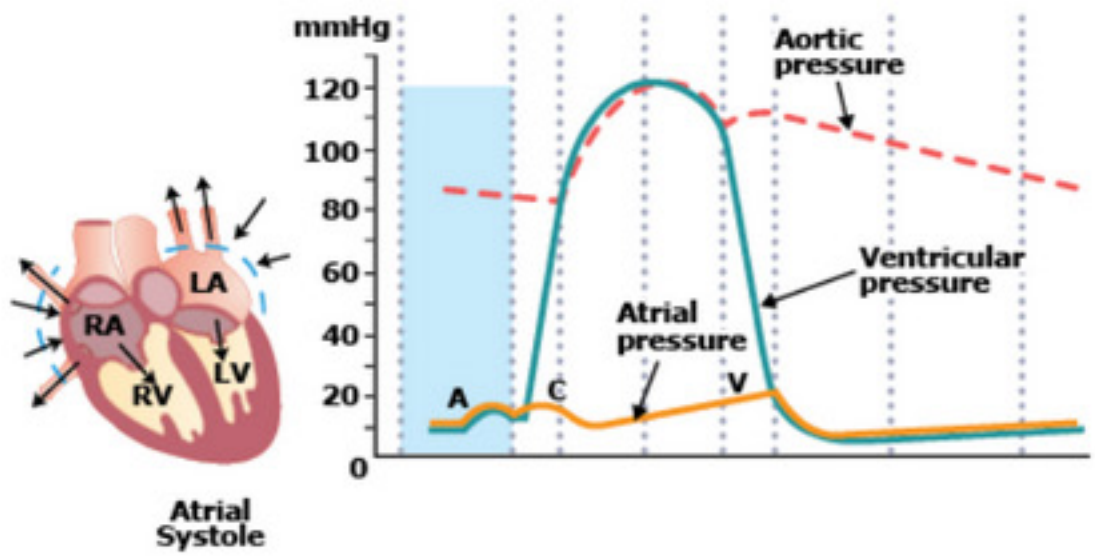
2 The Cycle Phases

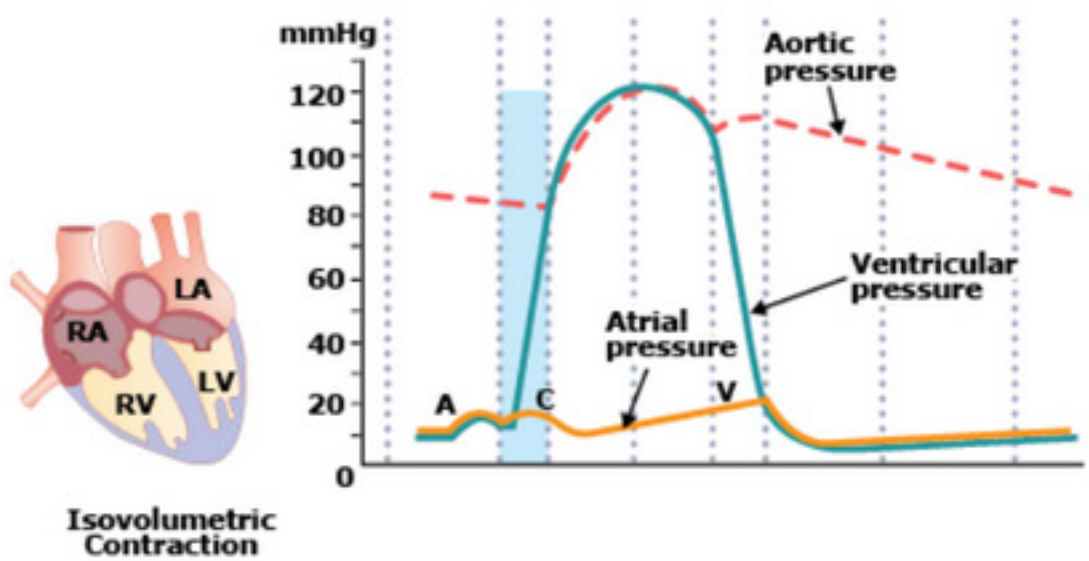
2.1 Late Diastolic Filling



▲ **Figure 14–2.1** Cardiac Cycle: Late Diastolic Filling

- Atrial contraction (S_4)
- "A wave" on the venous pulse
- Mitral valve open
- Minor contribution to LV filling at rest

2.2 Isovolumetric Contraction



▲ **Figure 14–2.2** Cardiac Cycle: Isovolumetric Contraction

- Ventricular depolarization (QRS)
- Ventricular contraction initiated
- Pressure in the ventricle rises about atrial pressure
- Closure of the mitral valve (S_1) and start of isovolumetric contraction
- Both mitral and aortic valves closed and pressure rising
- Ventricular volume constant = end-diastolic volume (EDV)

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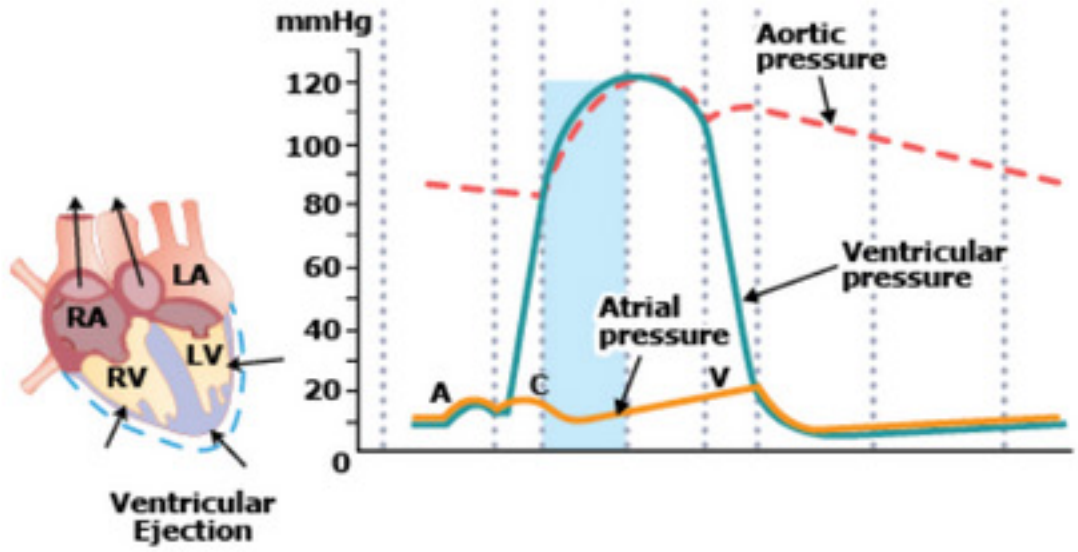
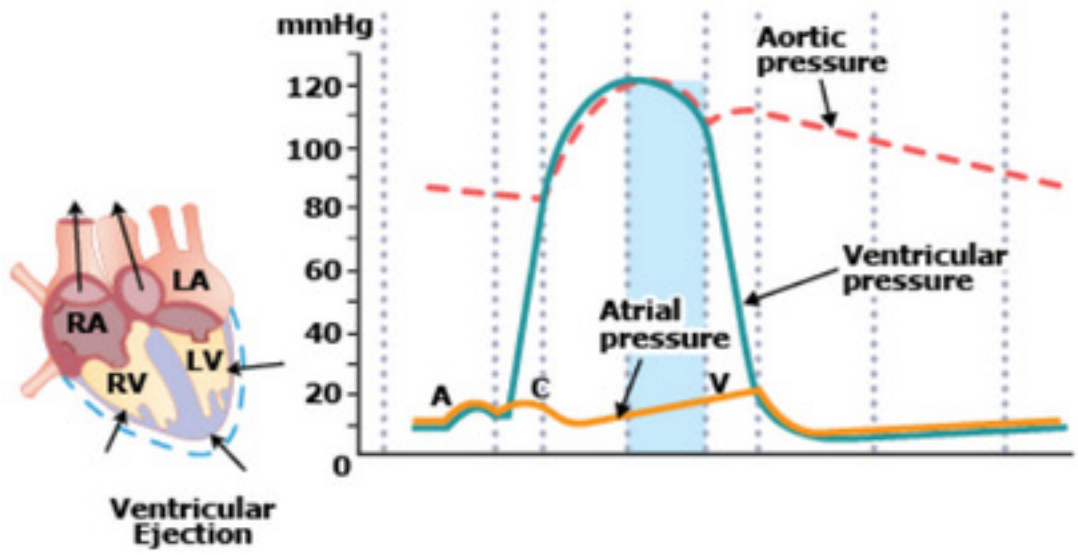
2.3 Ejection Phase



▲ **Figure 14–2.3A** Cardiac Cycle: Early Ejection Phase

- Aortic valve opens (diastolic blood pressure) because ventricular pressure exceeds aortic pressure
- Ejection phase begins
- Most of the blood ejected early in this phase (rapid ejection) when aortic and ventricular pressures are rising
- Peak ventricular pressure = peak aortic pressure (systolic blood pressure)



▲ **Figure 14–2.3B** Cardiac Cycle: Late Ejection Phase

- Reduced ejection as aortic and ventricular pressure starts to decline
- Volume ejected = stroke volume (SV), at rest about 50–60 mL, phase terminated when aortic valve closes (S_2)
- Creates dicrotic notch
- Aortic valve closes because ventricular pressure declines below aortic pressure.

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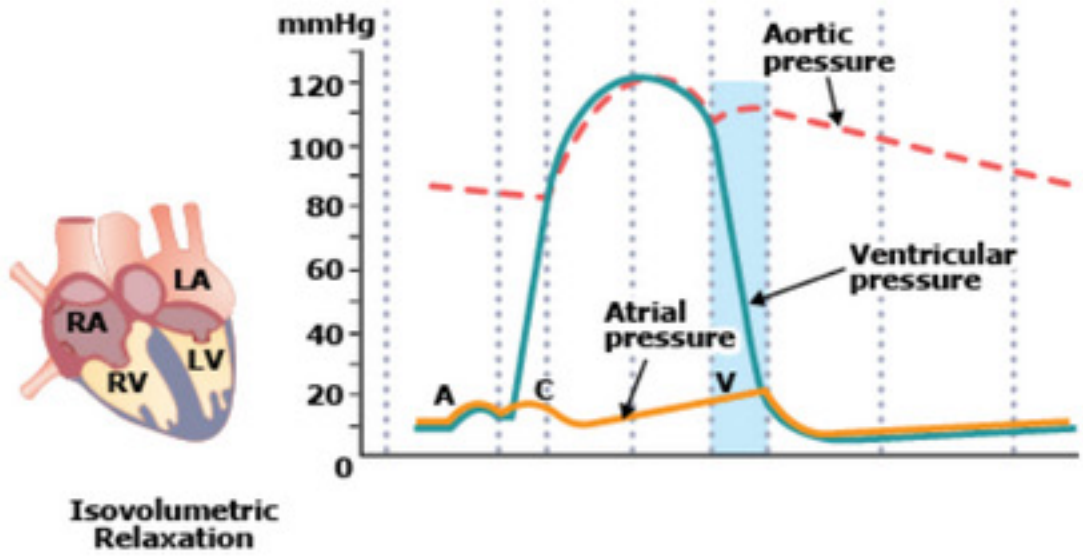
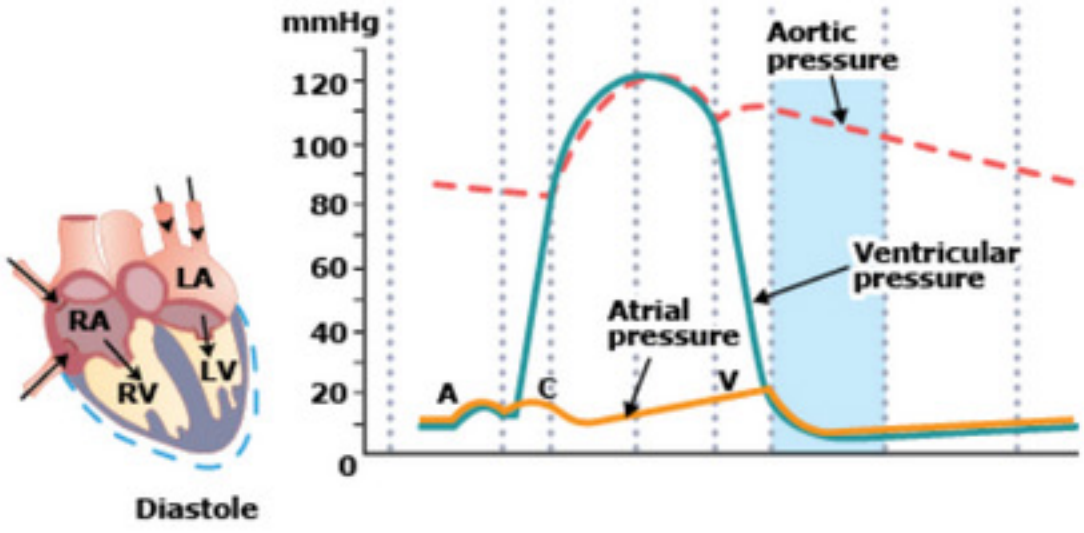
2.4 Isovolumetric Relaxation



▲ **Figure 14–2.4** Cardiac Cycle: Isovolumetric Relaxation

- Begins with closure of the aortic valve
- Both aortic and mitral valve closed, and pressure declines
- Ventricular volume constant = end-systolic volume (ESV)
- SV = volume of isovolumetric contraction (EDV) − volume of isovolumetric relaxation (ESV)
- EF (ejection fraction) = SV/EDV normal resting value 55–65%

2.5 Filling Phase



▲ **Figure 14–2.5A** Cardiac Cycle: Early Diastolic Filling

- Mitral valve opens because pressure in the ventricle decreases below atrial pressure.
- Phase begins with the ventricular muscle continuing to relax
- Rapid filling from the atrium and S_3, if present
- Final relaxation of the ventricle contributes to the rapid filling

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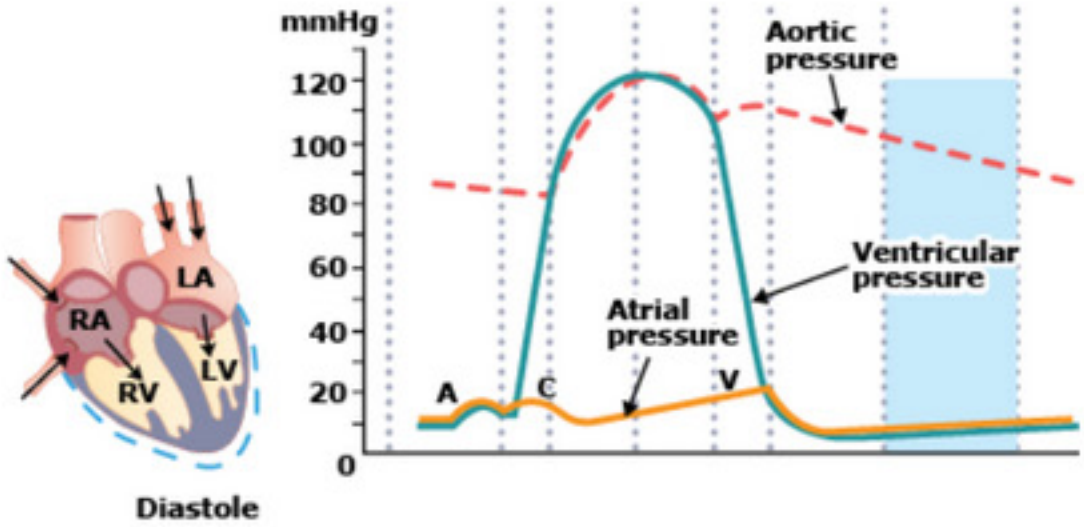

▲ **Figure 14–2.5B** Cardiac Cycle: Mid-diastolic Filling

- Period of reduced filling
- Ventricular filling in equilibrium with venous return
- Ventricular systole = isovolumetric contraction + ejection + isovolumetric relaxation, duration dependent on contractility
- Ventricular diastole = filling phase, duration dependent on heart rate

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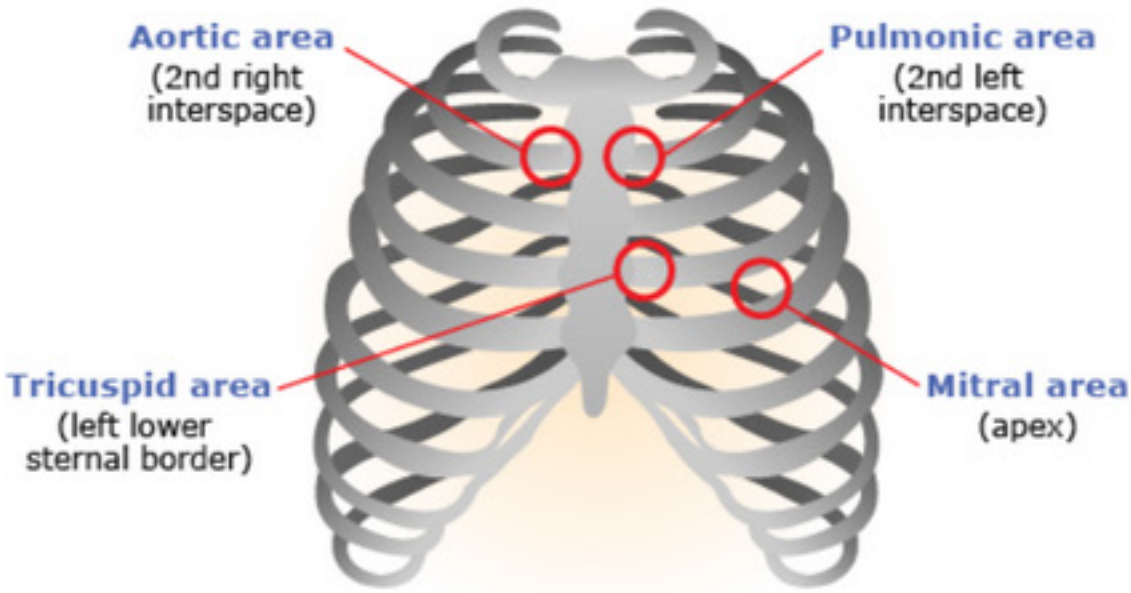
3 Cardiac Listening Posts



▲ **Figure 14–3.0** Cardiac Sounds: Listening Posts

4 Heart Sounds

- S_1 and S_2 are systolic sounds.
- S_3 and S_4 are diastolic sounds.
- Valves open right side, then left side, but close left, then right.
- A unilateral increase in the output of a ventricle delays the close of valves of S_2.
- Stenotic valves open slower and close more slowly (stay open longer).

4.1 First Heart Sound (S_1)

- Closure of mitral, then tricuspid valve.
- Caused by a vibrating turbulence of the blood and ventricular walls.
- Audible splitting may occur during inspiration.
- Fixed splitting with right bundle branch block. No splitting with left bundle branch block.

4.2 Second Heart Sound (S_2)

- Closure of the aortic, then the pulmonic valve
- Two components: **A_2**, aortic valve closure, and **P_2**, pulmonic valve closure.
- An audible splitting of the second sound occurs with a unilateral increase in the output of the right heart that delays the closing of the pulmonic valve, as in inspiration (physiological splitting) and atrial septal defect (flow from left to right).

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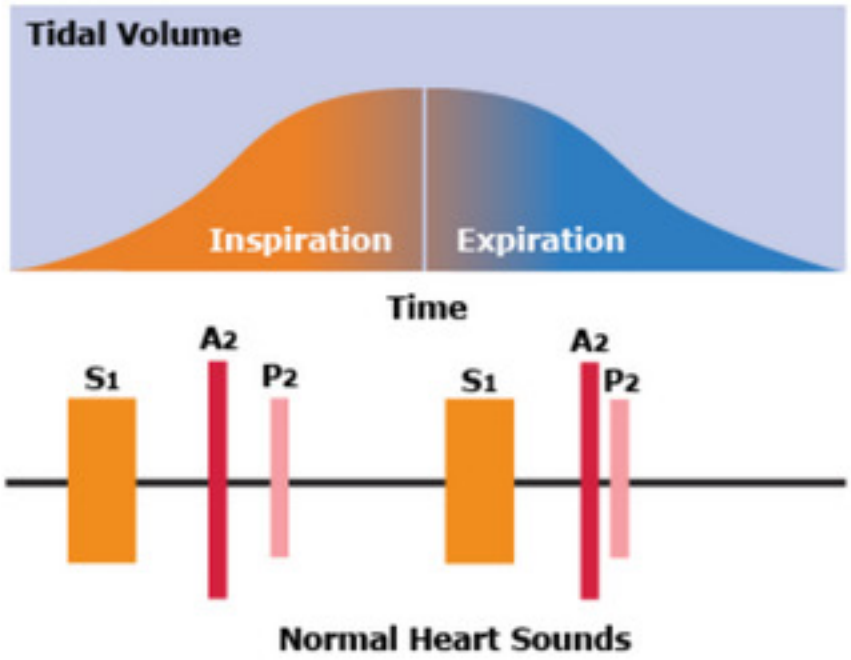

▲ **Figure 14–4.2** Systolic Sounds: Effect of Respiratory Cycle on S_2

- Similar audible splitting with right bundle branch block.
- Paradoxical splitting $P_2 \rightarrow A_2$ may occur with left bundle branch block and aortic stenosis.
- Accentuated with hypertension, diminished with stenosis.

4.3 Third Heart Sound (S_3)

- Occurs during the rapid filling of a very compliant ventricle.
- Normal in children and young adults.
- In older adults, a third heart sound is often associated with a volume-overloaded ventricle.
- A pathological S_3 is called a ventricular gallop.

4.4 Fourth Heart Sound

- Coincides with atrial contraction against a stiff ventricle (diastolic dysfunction), as seen in concentric hypertrophy, ventricular infarction.

4.5 Extra Sounds

- **Systolic:** Clicks heard mid or late systole are usually the result of systolic prolapse of the mitral or tricuspid valves. Often accompanied by valvular regurgitation.
- **Diastolic:** Opening snap of the mitral or tricuspid valve. Indicative of a stenosis.

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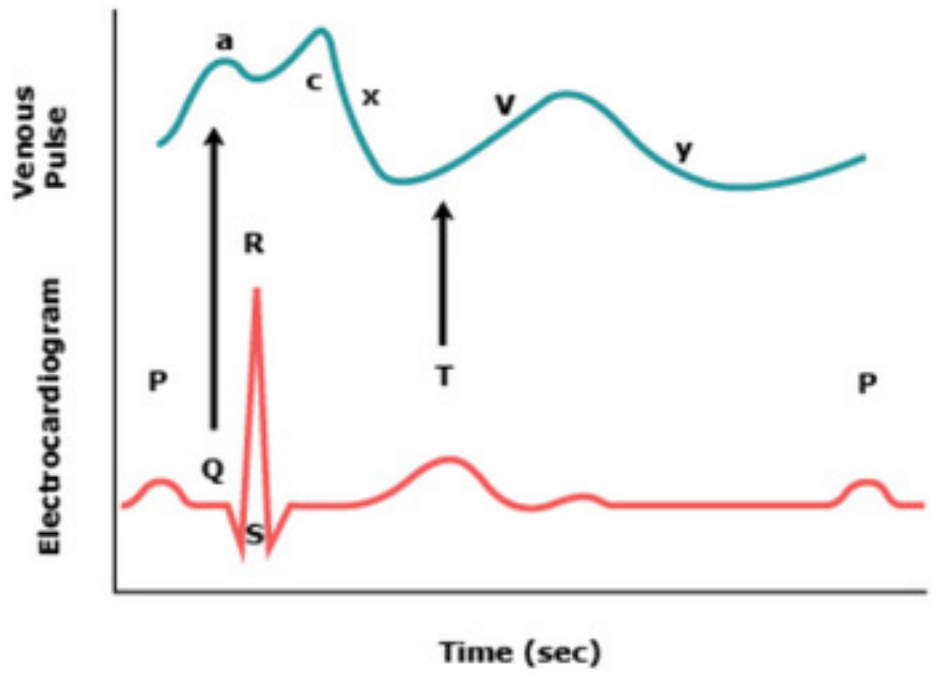
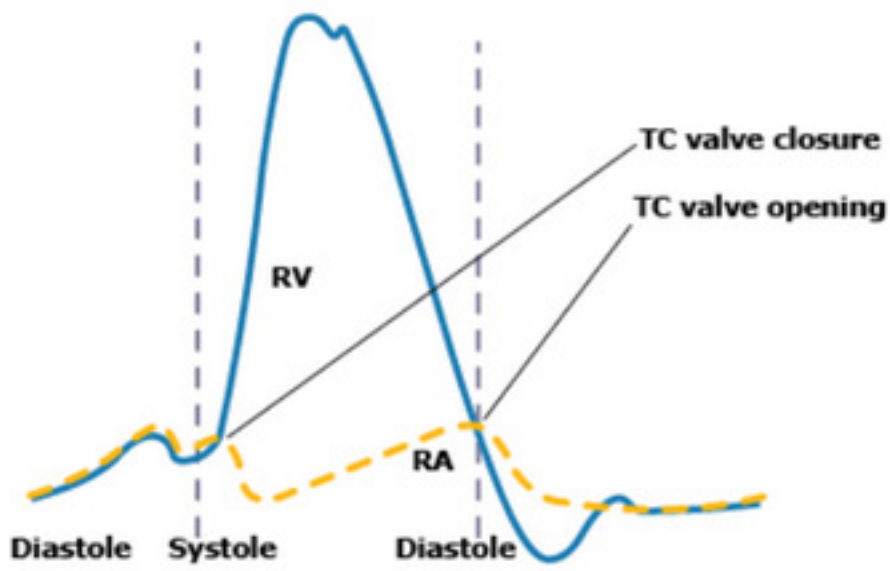
5 Systemic Venous Pulse



▲ **Figure 14–5.0A** Venous Pulse vs. EKG



RV = Right ventricular pressure
RA = Right atrial pressure (jugular pulse)
TC = Tricuspid Valve

▲ **Figure 14–5.0B** Cardiac Cycle: Right Heart

- Usually measured as the jugular venous pulsations (back pressures from right heart).
- Conditions that raise right-sided cardiac pressures elevate the pulse, such as heart failure, tricuspid valve problems.

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- **A wave:** due to right atrial contraction:
  - Correlates with the PR interval
  - Prominent in tricuspid disease
  - Absent with atrial fibrillation
- **X descent:** due to relaxation of the right atrium.
- **C wave:** interrupts the x descent and often not observed clinically.
- **V wave:** due to passive filling of the right atrium from systemic veins during ventricular systole (tricuspid valve closed):
  - Correlates with the T wave of EKG
  - Prominent with tricuspid insufficiency
  - Peak corresponds with the opening of the tricuspid valve
- **Y descent:** due to rapid flow of blood from the right atrium into the right ventricle:
  - Reduced slope in tricuspid stenosis

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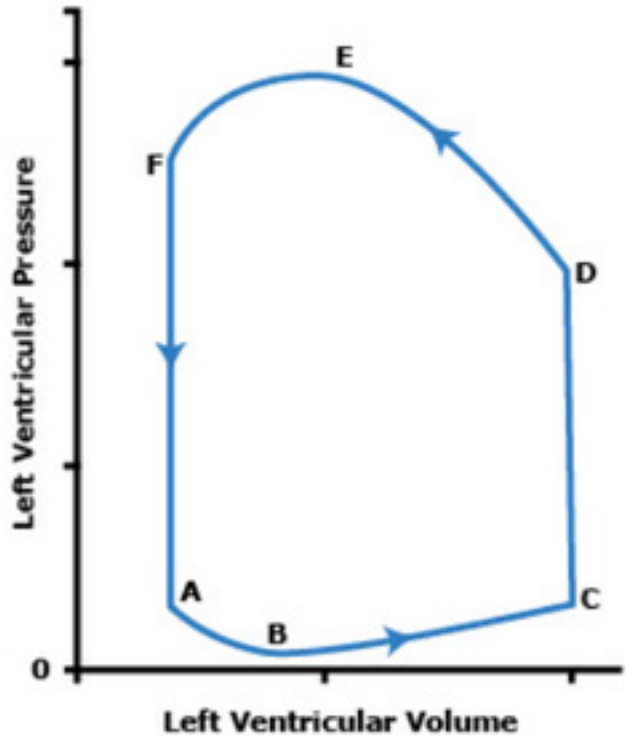
6 Pressure-Volume Loops

Pressure-volume loops depict the stroke work performed by the ventricle during each systole, the area within the loop. To follow the events in a cardiac cycle, the loop is read in a counterclockwise direction.



▲ **Figure 14–6.0** The Left Ventricular Pressure-Volume Loop

- Point A: Mitral valve opens to begin the filling phase.
- The initial drop in pressure to point B is due to the final relaxation of the ventricle as it begins to fill with blood.
- B → C shows a large increase in volume with only a slight increase in pressure. This is due to the very compliant nature of the ventricle. It is equivalent to the passive tension or preload curve mentioned previously. A diastolic dysfunction increases the slope of this line.
- Point C: Mitral valve closes, which is the beginning of isovolumetric contraction. Ventricle contains end-diastolic volume, and pressure is rising (vertical line). This is the most energy-demanding phase of the cardiac cycle.
- Point D: Aortic valve opens (diastolic blood pressure) to begin the ejection phase. Most of the blood is ejected early, point D → E.
- Peak pressure at E is ventricular systolic and systolic blood pressure. As pressure starts to decline, ejection continues to point F.
- Point D → F: Period when the ventricle performs the work of the cardiac cycle (work = pressure × volume, the area of the loop). But pumping the blood does not consume as much energy as pressurizing the blood.
- Point F: Aortic valve closes, creating the dicrotic notch to begin isovolumetric relaxation. Ventricle contains end-systolic volume and pressure is declining (vertical line).
- Point A: Opening of the mitral valve terminates isovolumetric relaxation.

Important Concept

An increase pressure work by the ventricle (hypertension) is more demanding than an equivalent increase in volume work (exercise). Thus the area within the loop is a good index of work, but is not a good index of the ventricle's energy demands.

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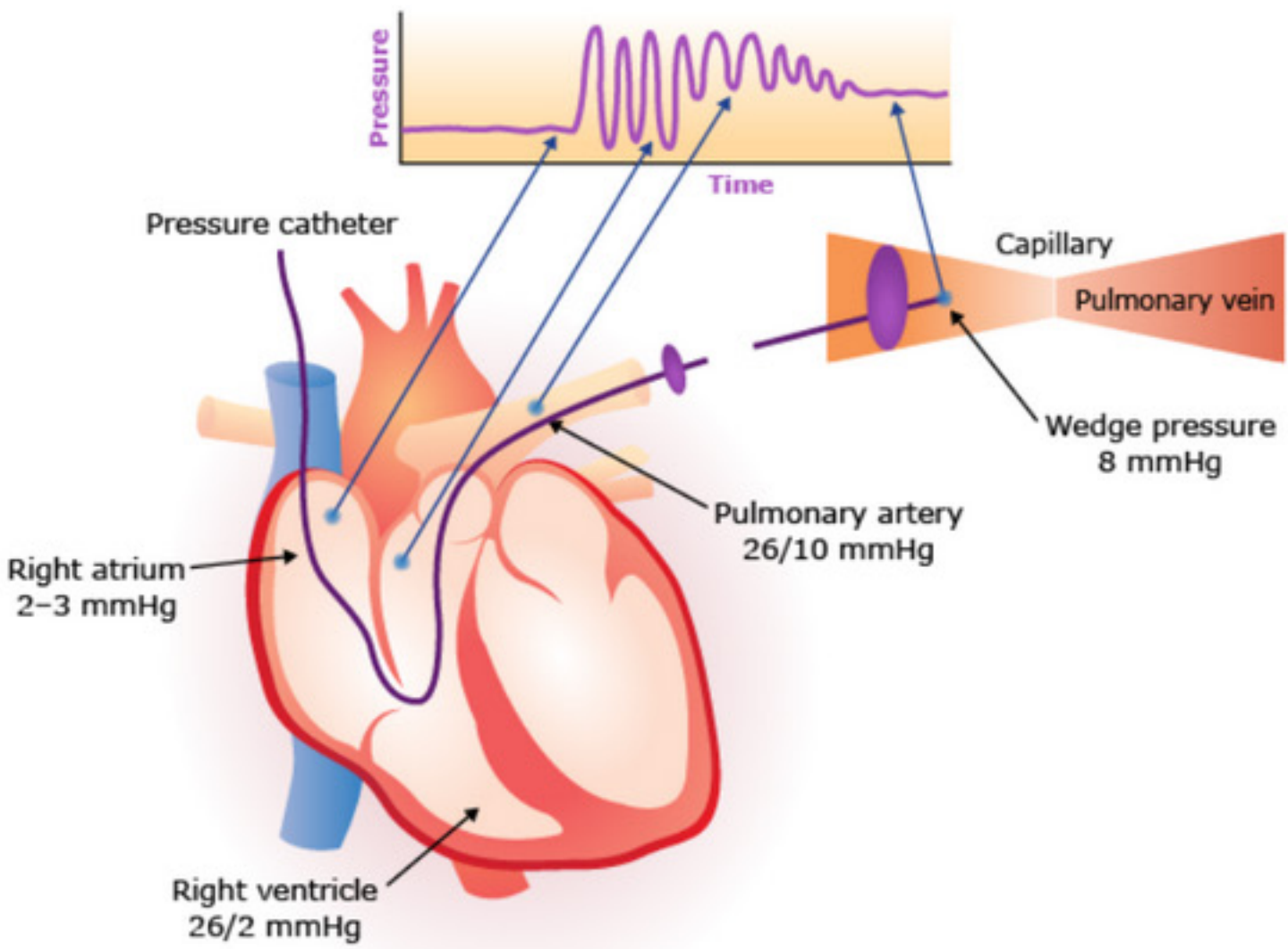
7 Pulmonary Wedge Pressure

- Pulmonary wedge pressure (pulmonary capillary wedge pressure) is measured by inserting a Swan-Ganz balloon-tipped catheter into the jugular vein and advancing it through the right atrium → right ventricle → and into the pulmonary artery. It is then advanced until the catheter tip is in a small pulmonary artery.
- The balloon is inflated (CO_2 or saline) to occlude the small artery.
- The pressure at the catheter tip falls and then stabilizes. This is the wedge pressure. It is considered very close to, and an index of, left atrial pressure.
- From the pulsations in the pressure recording, a left-sided *A wave* and *V wave* can be observed. These are equivalent to the systemic venous pulse recordings for the right heart.
- Pulmonary wedge pressure is an index of preload on the left ventricle except in mitral stenosis. It is elevated in left heart failure, mitral insufficiency, and mitral stenosis.
- The Swan-Ganz catheter is also useful in the evaluation of pulmonary hypertension, which is often caused by an elevated precapillary resistance. Pulmonary resistance can be calculated with pulmonary arterial pressure, wedge pressure, and a value for cardiac output (see 11-7).



▲ **Figure 14–7.0** Insertion of a Swan-Ganz Catheter

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1 Valvular Heart Disease

1.1 Mitral Stenosis

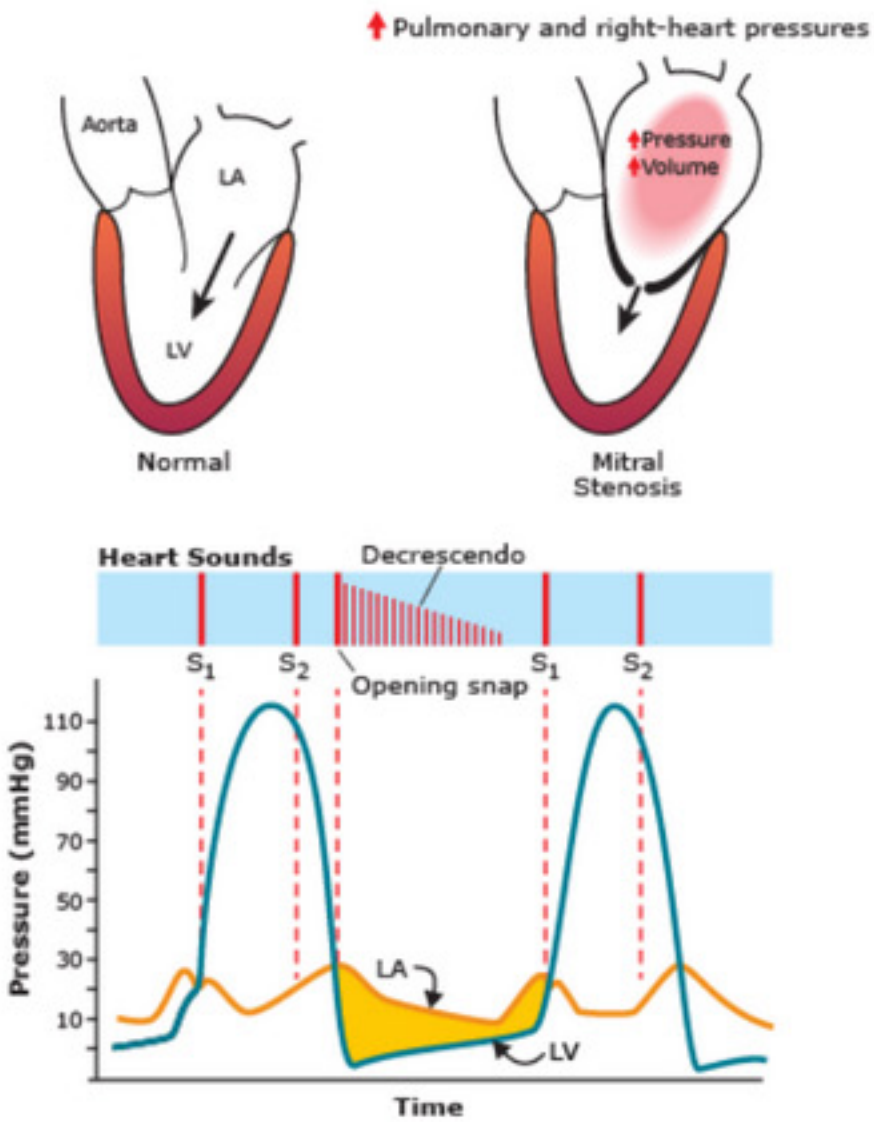
- Most common cause is rheumatic fever.
- Opening problem, mitral valve acts as a resistance point, creating a pressure gradient between the left atrium and ventricle during filling phase.
- ↑ left atrial pressure and dilated atrium, which can lead to atrial fibrillation.
- ↑ pulmonary venous, ↑ capillary (edema, dyspnea), ↑ pulmonary arterial pressures.
- Pulmonary hypertension can involve ↑ arteriolar resistance as well.
- Right heart enlargement and hypertrophy.
- Left ventricle of normal or reduced size.
- Murmur: diastolic; opening snap after S_2, followed by a low-frequency decrescendo murmur (diastolic rumble).

Important Concept

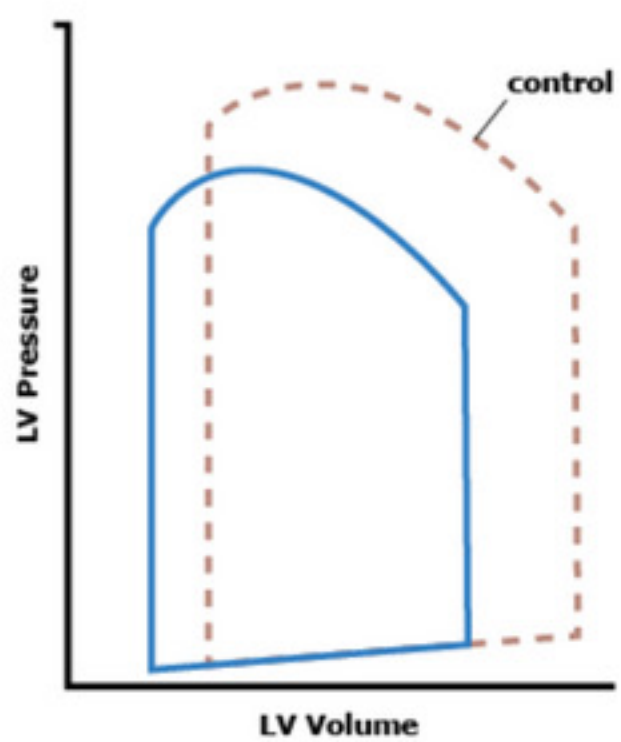
Left atrium is enlarged, but the left ventricle is of normal or reduced size.

Important Concept

Pressure volume curve is not diagnostic for mitral stenosis. It simply shows a smaller-than-normal left ventricle (loop shifted to the left). It could represent other states, such as hemorrhage.



▲ **Figure 15–1.1A** Mitral Stenosis: Hemodynamics



▲ **Figure 15–1.1B** Mitral Stenosis: Pressure-Volume Loop

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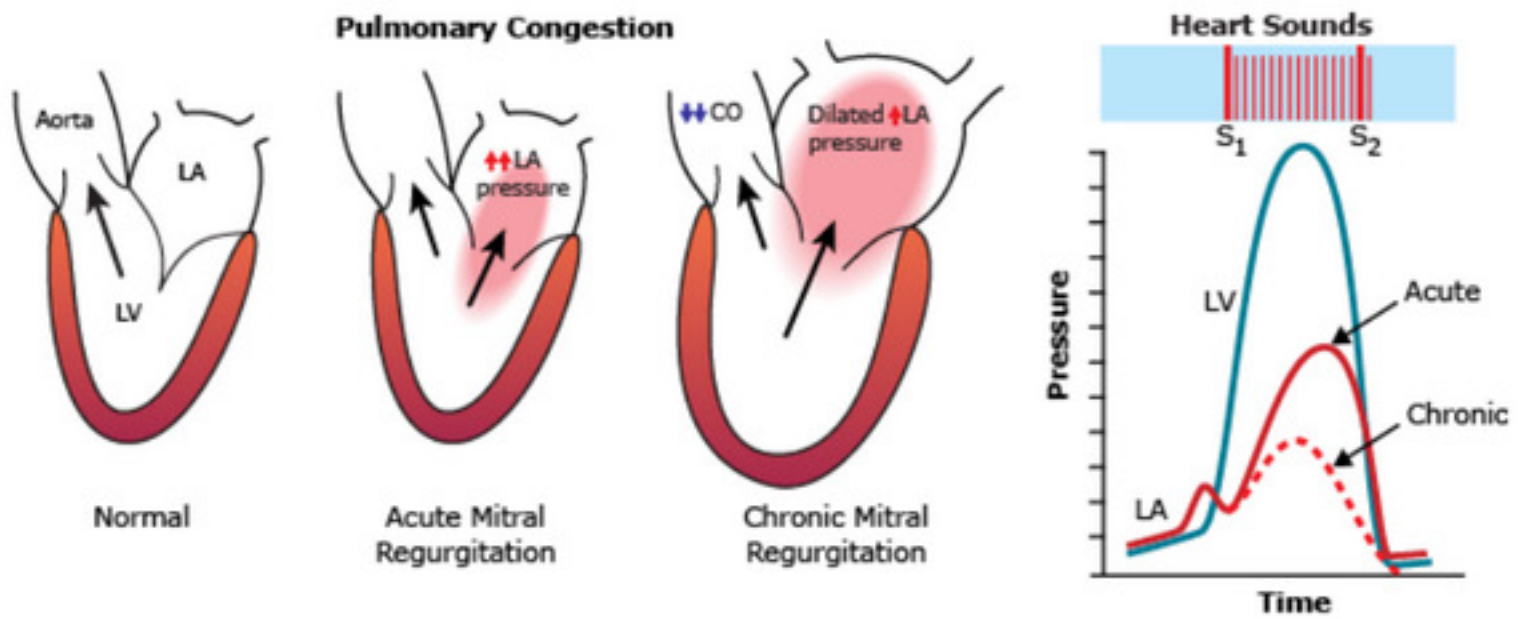
1.2 Mitral Regurgitation

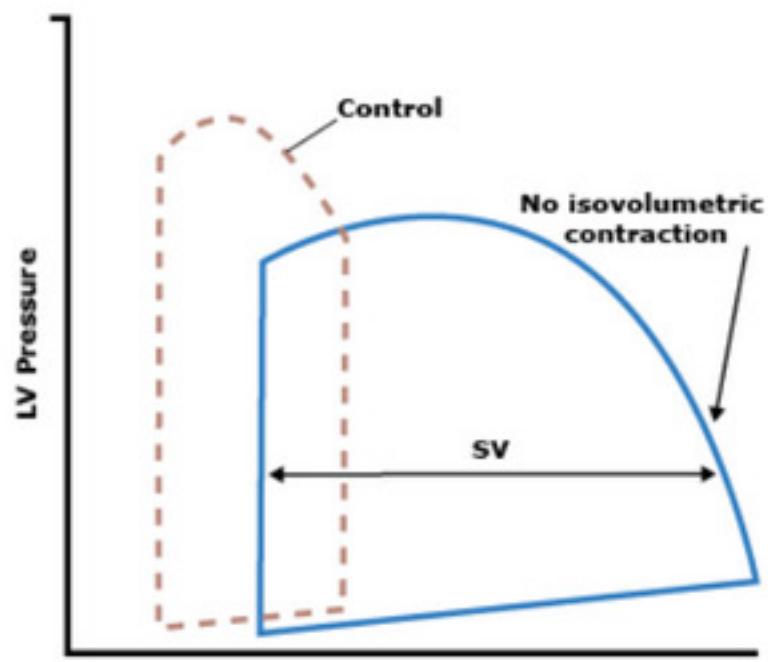


▲ **Figure 15–1.2A** Mitral Insufficiency: Hemodynamics

- Closing problem, can involve valve leaflets, mitral annulus, chordae tendineae.
- Part of left ventricular stroke volume is delivered retrograde into the left atrium.
- No isovolumetric contraction (blood flow from the left ventricle to atrium).
- Stroke volume to aorta less than total stroke volume.
- High left atrial pressure acute, decreasing with atrial enlargement chronically to only a modest pressure elevation above normal.
- Reduced atrial pressure chronically causes ↑ % of stroke volume to atrium.
- Acute: atrium normal size but ↑↑ atrial pressure, ↑ pulmonary pressures (congestion, edema).
- Chronic: atrium enlarged, ↑ atrial pressure, reduced pulmonary involvement, ↑ % stroke volume to atrium, ↓ cardiac output.
- Stroke volume to atrium returns to ventricle in diastole (volume cycles between ventricle and atrium).
- Volume overload (increased preload), dilation, and eccentric hypertrophy of ventricle.
- Murmur: systolic, begins at S_1 and continues to S_2, holosystolic (pansystolic).

Important Concept

Both the left atrium and ventricle are enlarged.



▲ **Figure 15–1.2B** Mitral Insufficiency: Pressure-Volume Loop

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1.3 Mitral Valve Prolapse

- Common and usually asymptomatic, ballooning of the mitral valve leaflets into the left atrium during ventricular systole.
- Sometimes accompanied by mitral regurgitation.
- Identified as a mid-systolic click and late systolic murmur.
- Clinical case is most often benign.

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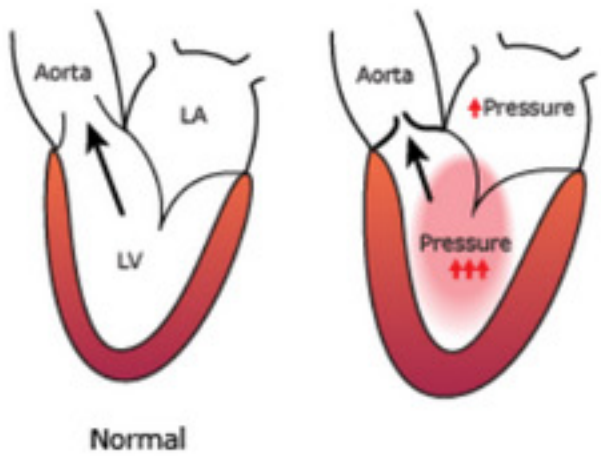
2 Aortic Stenosis

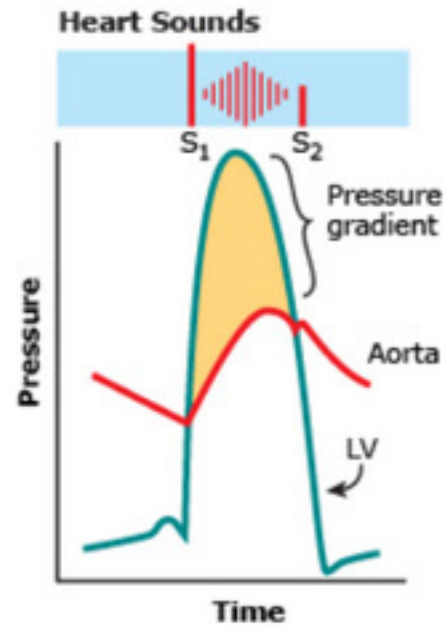
- Opening problem, often caused by degenerative calcific changes in the valve leaflets.
- Valve area reduced and acts as a major resistant point.
- Pressure decreases as blood ejected into the aorta.
- Advanced state > 100 mmHg pressure gradient across the valve during ejection.
- Left ventricular systolic pressure increases to overcome resistance to flow (↑ afterload).
- Pressure overload leads to a concentric ventricular hypertrophy, reduced chamber size, and a diastolic dysfunction.
- Left atrium enlarges, hypertrophies, and atrial contraction a more important role in ventricular filling due to diastolic dysfunction (prominent "A wave").
- Atrial fibrillation creates a problem with ventricular filling.
- Initially ventricular hypertrophy assists ejection, but eventually leads to a systolic dysfunction.
- Aortic pressure normal in the early stages, but decreases in later stages.
- Advanced stage: angina, exertional syncope, congestive heart failure.
- Murmur: systolic; begins after S_1 with a crescendo-decrescendo in intensity.

Generalization: A pressure overload (*aortic stenosis*, hypertension) is well tolerated short-term, but poorly tolerated long-term. Initially, there is no increase in preload, with the increased performance the result of an increased contractility. Compensatory concentric hypertrophy develops, with a greatly thickened ventricular wall, reduced chamber size and associated diastolic dysfunction. Eventually, systolic dysfunction develops, with ventricular failure.

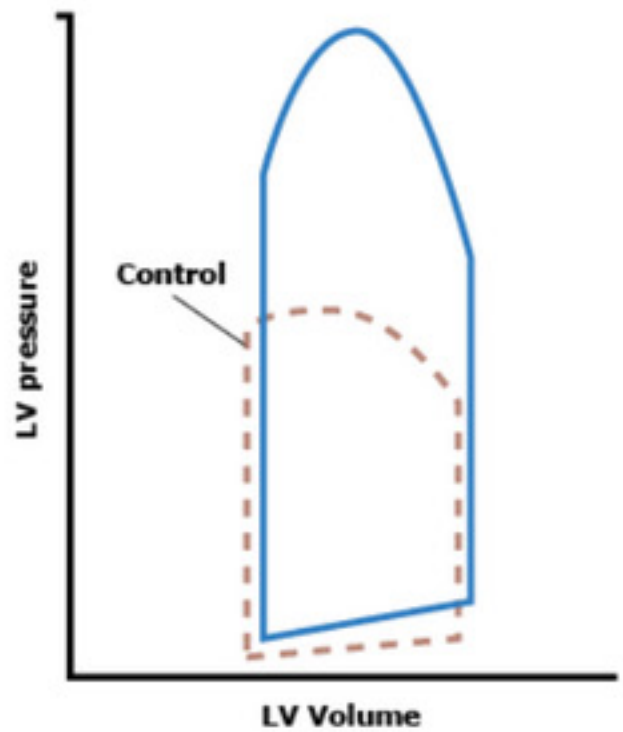
Important Concept

The most defining characteristic is that left ventricular systolic pressure is significantly higher than aortic systolic pressure.





▲ **Figure 15–2.0A** Aortic Stenosis: Hemodynamics



▲ **Figure 15–2.0B** Aortic Stenosis: Pressure-Volume Loop

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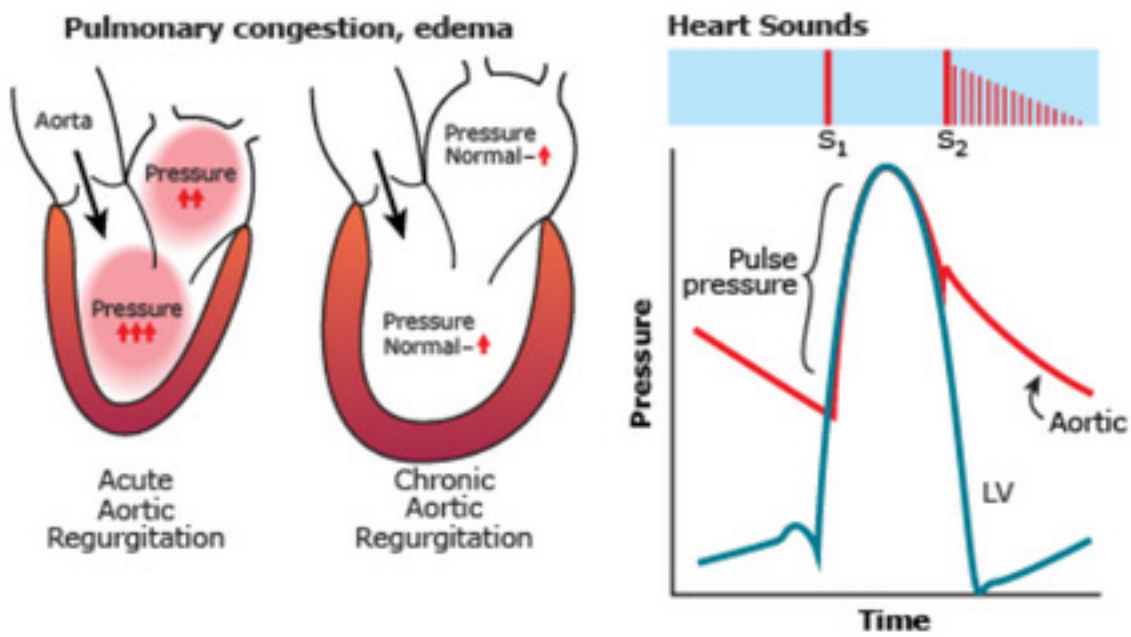
2.1 Aortic Regurgitation

- Closing problem, with retrograde flow from the aorta to left ventricle.
- No isovolumetric relaxation—increasing volume of ventricle from aortic backflow.
- Acute regurgitation: normal-sized left ventricle, ↑ volume, ↑ diastolic ventricular pressure, ↑ left atrial and pulmonary pressures, pulmonary congestion, and edema (medical emergency).
- Chronic regurgitation: compensatory dilation and eccentric hypertrophy—"large" compliant ventricle, no diastolic dysfunction—↓ retrograde pressure transmission to pulmonary circuit.
- ↑↑ ventricular diastolic volume but only a slight increase in diastolic pressure.
- Many patients asymptomatic for years, but eventually systolic dysfunction occurs.
- ↑ stroke volume with retrograde flow produces ↑ systolic blood pressure, but – ↓↓ in diastolic blood pressure = ↑↑ pulse pressure.
- Increased ventricular wall stress with decreased coronary perfusion pressure in diastole can induce angina in the absence of coronary artery disease.
- Murmur: diastolic; decrescendo that begins at S_2.

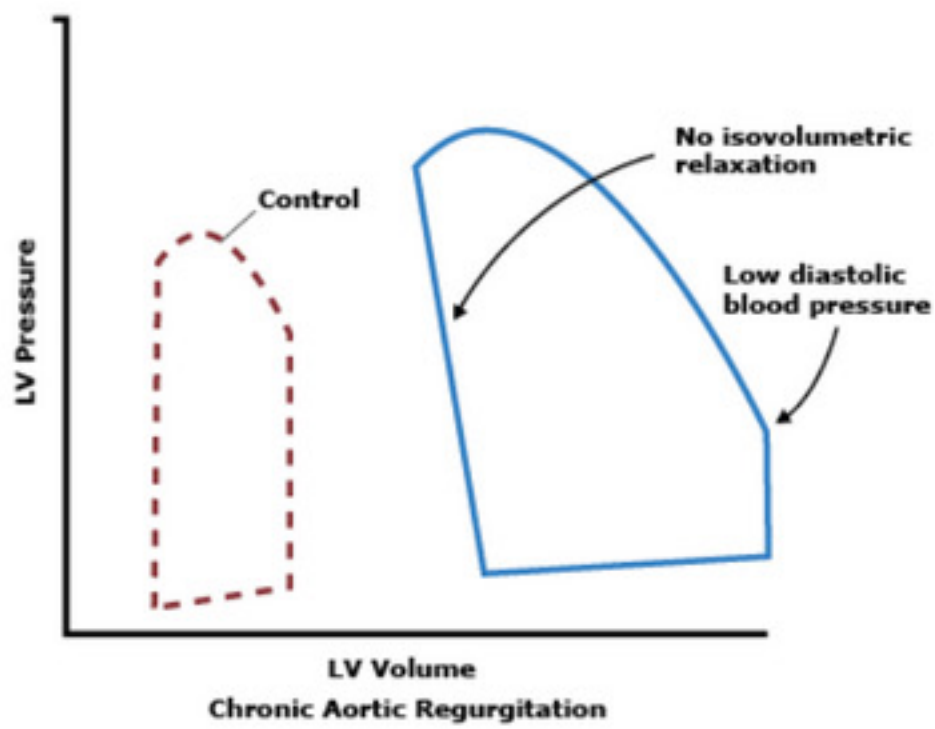
Important Concept

The most characteristic feature is a very low diastolic blood pressure with a very high pulse pressure.



▲ **Figure 15–2.1A** Aortic Reguritation: Hemodynamics

Generalization: A large volume overload (aortic and mitral regurgitation, patent ductus) is often poorly tolerated acutely, but if it develops gradually, is often well tolerated chronically. Chronic adaptation is chamber enlargement and an eccentric hypertrophy, with a modest increase in wall thickness. Compliance is maintained with no diastolic dysfunction and reliance on Frank-Starling for increased performance. Failure is usually associated with a systolic dysfunction. The right ventricle differs from the left in that, acutely, a volume overload is better tolerated than a pressure overload.



▲ **Figure 15–2.1B** Aortic Regurgitation: Pressure-Volume Loop

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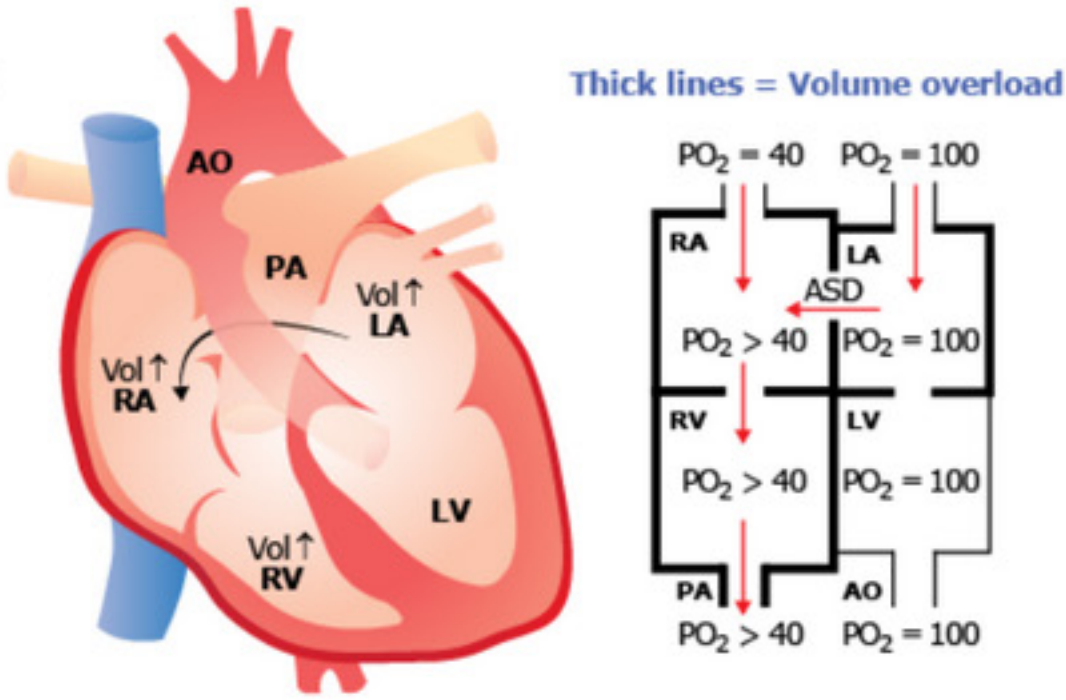
3 Shunting of Blood

3.1 Atrial Septal Defect (ASD)

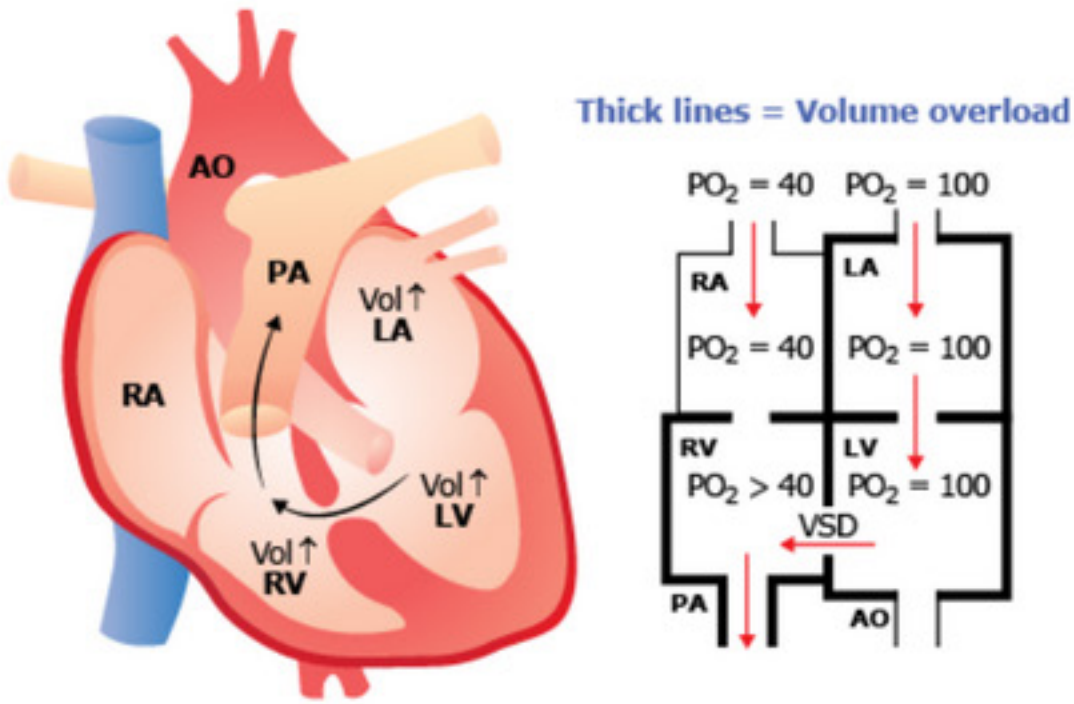
- Equivalent to patent foramen ovale.
- Pressure generally higher in the left heart than in the right heart.
- Blood flow left atrium → right atrium (no cyanosis), (L → R shunt).
- Blood PO_2 of RA, RV, pulmonary artery > systemic venous.
- Volume overload and enlargement of the RA and RV.
- Output of right heart > left heart.
- Diagnosed via blood oximetry.
- Pulmonary disease and ↑ pulmonary pressure cause shunt reversal (right → left, cyanosis).



▲ **Figure 15–3.1** Atrial Septal Defect: Hemodynamics

3.2 Ventricular Septal Defect (VSD)

- Opening in the intraventricular septum.
- Blood flow LV → RV (L → R shunt).
- Volume overload on RV, pulmonary circulation, LA, LV; chamber dilation.
- RV PO_2 > RA PO_2.
- Pulmonary vascular disease ↑ pressure in the right heart and may reverse the shunt (R → L shunt, cyanosis).



▲ **Figure 15–3.2** Ventricular Septal Defect: Hemodynamics

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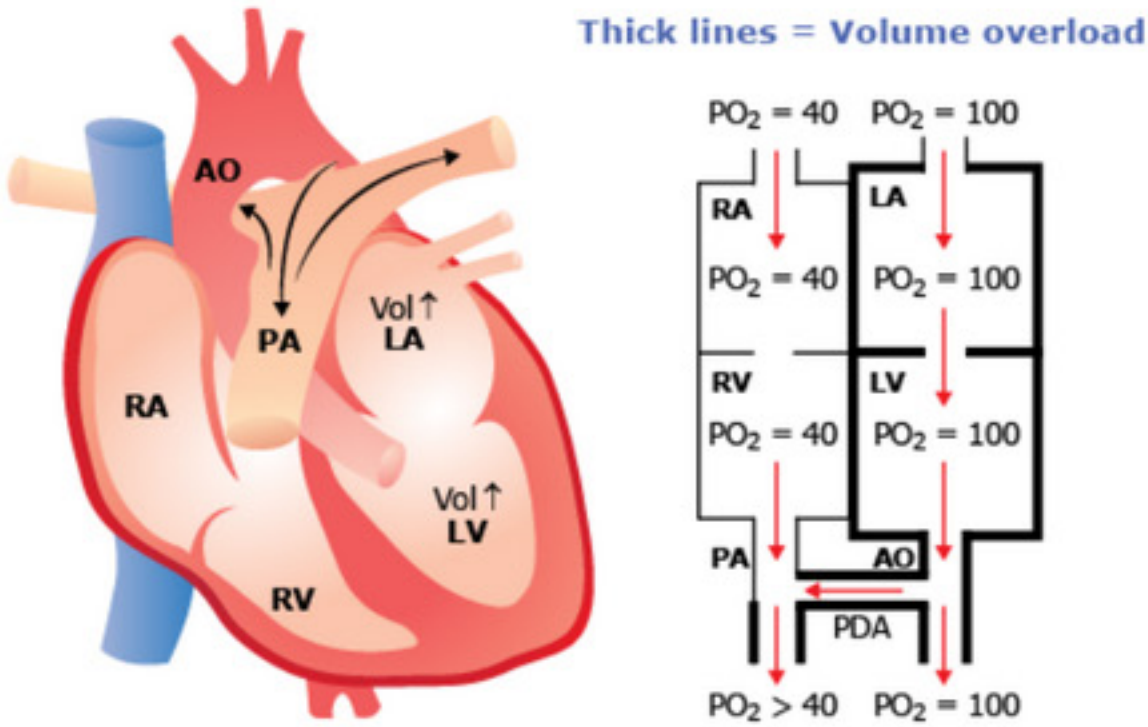
3.3 Patent Ductus Arteriosus

- Connects the pulmonary artery to the descending aorta.
- Constricts after birth due to ↑ PO_2 of blood passing through and ↓ prostaglandins.
- Shunt between the aorta and pulmonary artery (left-to-right shunt no cyanosis).
- Volume overload on left atrium and ventricle.
- Swan-Ganz: PO_2 = 40 in systemic vein, RA, RV; PO_2 > 40 pulmonary artery.
- Pulmonary vascular disease and ↑ pulmonary arterial pressure shunt reverses (right-to-left shunt—Eisenmenger syndrome).
- Lower body cyanosis; upper body normal.
- Murmur: Continuous, machine-like murmur best heard at the left subclavian region.



▲ **Figure 15–3.3** Patent Ductus: Hemodynamics

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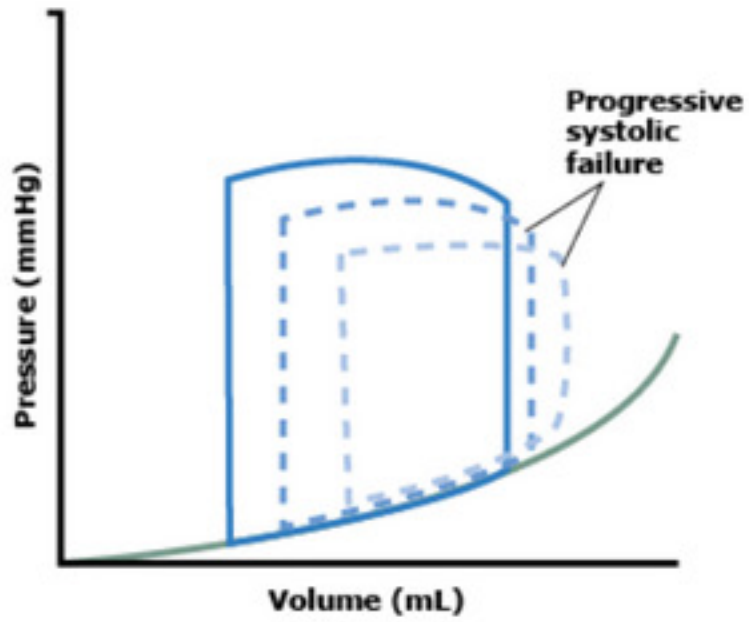
4 Heart Failure

- Defined by any situation in which the heart does not pump the venous return, as evidenced by venous pooling and elevated ventricular filling pressure.
- Systolic dysfunction (failure): Failure to maintain output because of an inability to elevate contractility (contractility failure). This includes situations such as excessive afterload.
- Diastolic dysfunction (failure): Failure related to abnormalities in diastolic relaxation or structural decreases in muscle compliance (Frank-Starling failure).
- Most heart failure patients demonstrate systolic failure; a predominant diastolic failure is much less common.

4.1 Left Ventricular Systolic Failure

- ↓ contractility, ↓ ejection fraction, ↓ SV, ↑ ESV, ↑ preload
  - The increased preload is an inherent adaptation to partially compensate for the loss of contractility.
  - Pressure-volume loop shifts to the right, venous pooling and pulmonary congestion.



▲ **Figure 15–4.1** Left Ventricular Systolic Failure: Pressure-Volume Loop

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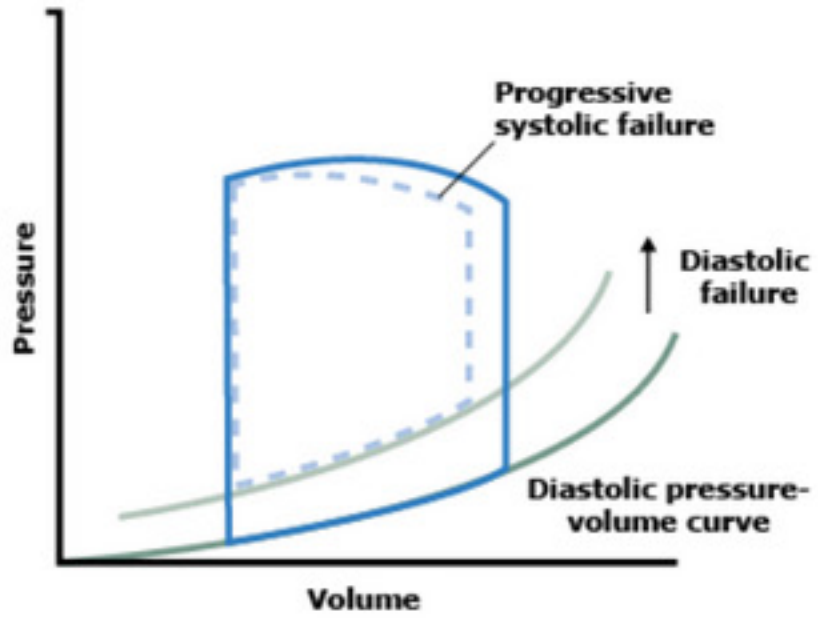
4.2 Left Ventricular Diastolic Failure

- Filling phase at higher than normal ventricular pressure.
  - Pressure-volume loop shifted upward = decreased compliance
  - Venous congestion



▲ **Figure 15–4.2** Left Ventricular Diastolic Failure: Pressure-Volume Loop

- *Neurohumoral* compensation (short-term *compensatory;* long-term *contributes to failure*).
  - ↑ Sympathetic adrenergic: ↑ TPR, venoconstriction, ↑ β_1 of heart muscle, ↑ renin.
  - ↑ renin-AII-aldosterone: ↑ TPR, ↑ blood volume (↑ preload).
  - ↑ ADH: ↑ blood volume (↑ preload).
  - ↑ endothelin: ↑ TPR.
- ↑ TPR will ↑ afterload and the work of the heart, promoting ↓ CO.
- ↑ Continuous sympathetic activity causes down-regulation of β_1 receptors and up-regulation of inhibitory G-proteins that ↓ inotropic response.
- Current therapy (see cardiac muscle) involves combinations of diuretics, vasodilators, and β blockers.

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Unit 6

Pulmonary Physiology

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1 Anatomy

1.1 Airways

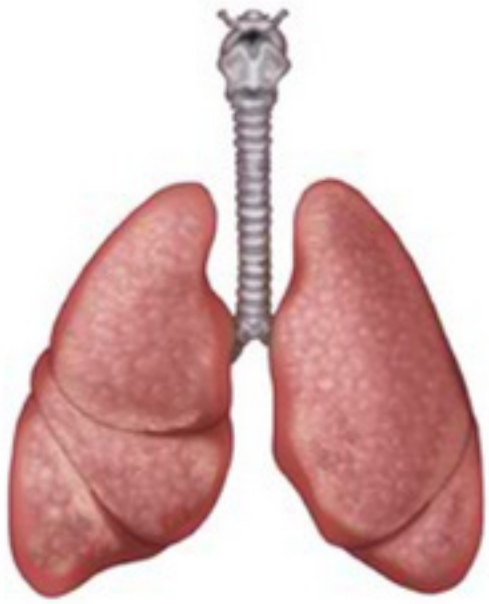
- Trachea
- Bronchi

1.2 Lobes

- Left: Upper and lower
- Right: Upper, middle, and lower

1.3 Pleura

- Visceral: Adheres to lung surface
- Parietal: Adjacent to chest wall
- Pleural Space: Contains a thin film of fluid
  - Allows the two pleural surfaces to slide past each other but prevents them from separating. Can be filled with air (pneumothorax), fluid (pleural effusion), or blood (hemothorax).



▲ **Figure 16–1.1** Gross Lung Structure

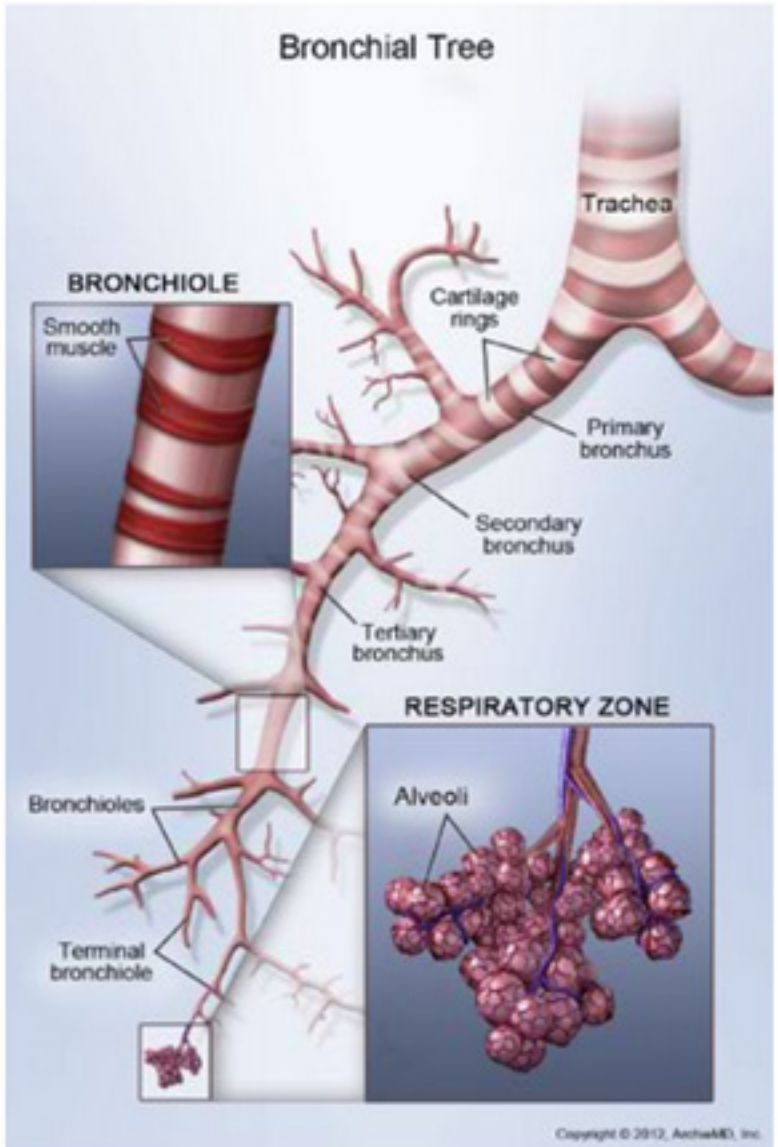
1.4 Airway Zones

1.4.1 Upper Respiratory (Conducting Zone)

- Columnar epithelium, ciliated cells, goblet cells
- Functions: Warms, humidifies air, deposes particles, maintains mucociliary clearance
- Airways: Pharynx, trachea, bronchi, bronchioles, terminal bronchioles
- Diseases occur when mucociliary clearance is disrupted, as in cystic fibrosis, immotile cilia syndromes.

1.4.2 Lower Respiratory (Respiratory Zone)

- Specialized respiratory epithelium (squamous), large surface for gas exchange
- Airways: Respiratory bronchioles, alveolar ducts, alveoli



▲ **Figure 16–1.4** Airway Zones

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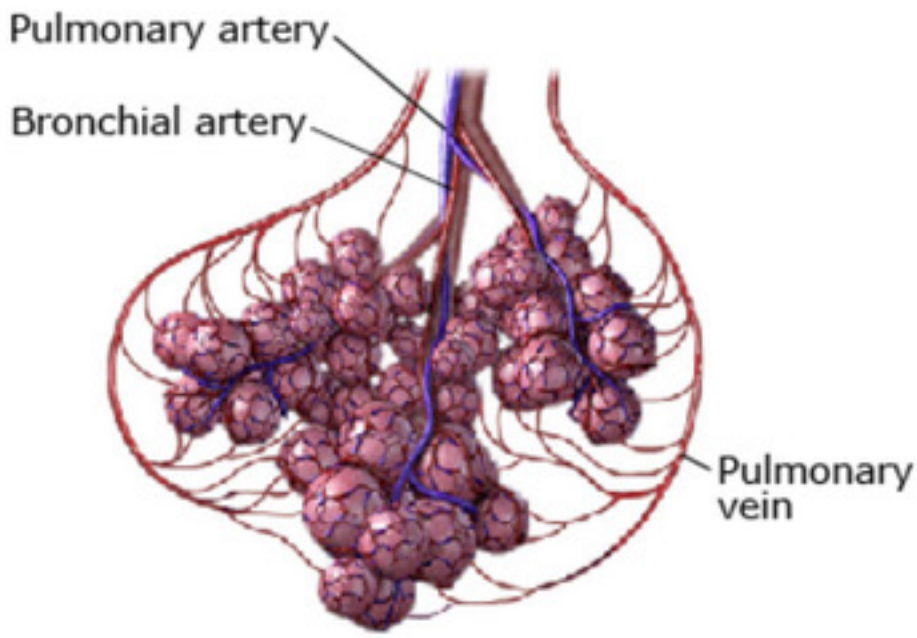
2 Blood Supply

Bronchial Arteries: Arise from the aorta and supply larger airways.

Pulmonary Arteries: Deoxygenated blood from the right side of the heart.

Pulmonary Capillaries: Extremely large surface area to facilitate gas exchange. Blood flow often described as a thin sheet of fluid surrounding the alveoli.



▲ **Figure 16–2.0** Blood Supply in the Terminal Airways and Alveoli

3 Innervation of Airways

Airway diameter is a function of the balance between sympathetic and parasympathetic inputs. This is one of the major focuses in therapy for airway diseases.

3.1 Sympathetic

- β_2 receptors
- Activation leads to relaxation of bronchial smooth muscle and bronchial dilation

3.2 Parasympathetic

- M_3 muscarinic receptors
- Activation leads to contraction of bronchial smooth muscle and bronchoconstriction

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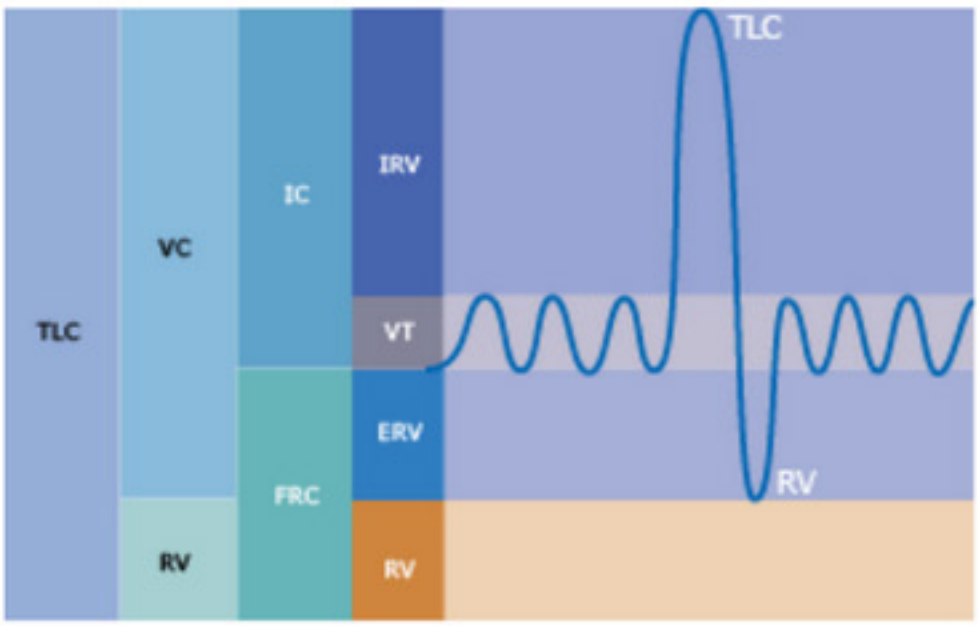
1 The Lungs



▲ **Figure 17–1.0** Relationships Among Lung Volumes and Capacities

1.1 Lung Volumes

Tidal Volume (V_T): Volume of air inspired/expired at rest (500mL is a good average).

Residual Volume (RV): Volume of air remaining in the lungs after a maximal expiration.

Inspiratory Reserve Volume (IRV): Maximum volume of air that can be inspired above resting tidal volume.

Expiratory Reserve Volume (ERV): Maximum volume of air that can be expired after a resting expiration.

Of the four volumes, *tidal volume* and *residual volume* are the most important for disease pattern recognition.

1.2 Lung Capacities

Functional Residual Capacity (FRC): The amount of air in the lung system at the end of an expiration at rest (glottis open, all respiratory muscles relaxed). It is also considered the neutral, or equilibrium state, of the respiratory system. ERV + RV

Vital Capacity (VC): Maximum amount of air expired following a maximal inspiration. If done forcefully, *Forced Vital Capacity*.

$$VC = ERV + V_T + IRV$$

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Total Lung Capacity (TLC): The volume of air in the lung system after a maximal inspiration.

$$TLC = VC + RV$$

Inspiratory Capacity (IC): Maximal inspiration from FRC.

$$IC = V_T + IRV$$

The three clinically important capacities are: FRC, VC, TLC.

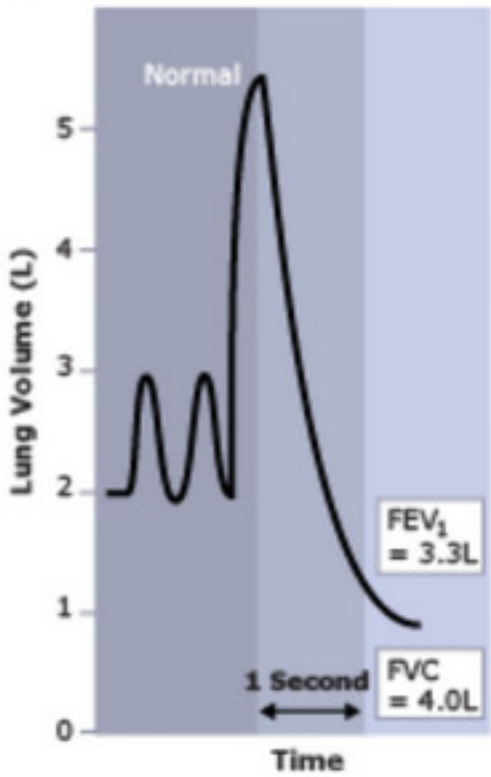
1.3 Spirometry

Spirometry measures only changes in lung volume and flow (volume/time). It cannot measure RV or any capacity containing RV (TLC, FRC). Measurement of FRC requires an indirect method, either helium dilution or body plethysmography.

1.3.1 Pulmonary Function Testing (FVC)

Three important data values obtained: FVC, FEV_1 (volume expired in the first second), FEV_1/FVC (normally 0.8).

Significantly, during the forced maximal expiration in this test, there is a partial collapse of the larger airways. This increases airway resistance and limits the maximum flow rate. Once the partial collapse has occurred, air flow becomes effort independent. This makes the test very reproducible. The partial collapse is called *Dynamic Compression* of the airways.



▲ **Figure 17–1.3A** Pulmonary Function Test: Spirometry

1.3.2 Two Major Patterns of Disease

Obstructive: TLC is normal or above normal; no problem with inspiration. In a forced maximal expiration, a small volume is slowly expired. Asthma, COPD.

Restrictive: TLC is below normal; main problem is inspiration. In a forced maximal expiration, a small volume is quickly expired and to a reduced RV. This applies to restrictive diseases characterized by an increase in the lung's elastic recoil. Pulmonary fibrosis, interstitial lung diseases.

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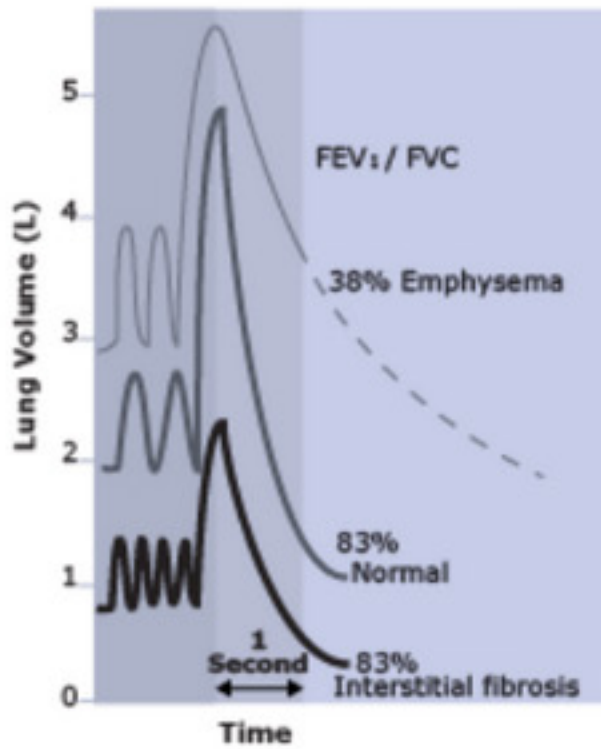
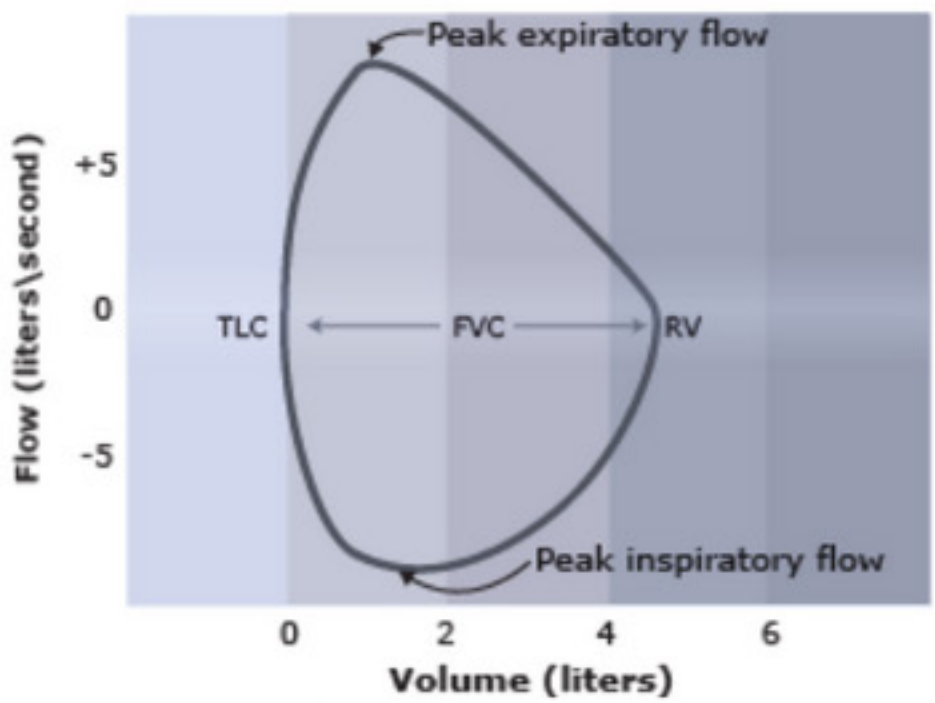
Obstructive Disease		Restrictive Disease	
TLC	normal or ↑	TLC	↓
FVC	↓	FVC	↓
FEV_1	↓↓	FEV_1	↓
FEV_1/FVC	↓	FEV_1/FVC	normal
FRC	↑	FRC	↓
RV	↑	RV	↓



▲ **Figure 17–1.3B** Spirometry: Obstructive vs. Restrictive Pattern

1.3.3 Volume Loops

The graphic depiction of flow versus lung volume during a maximal expiration from TLC can also separate obstructive versus restrictive lung diseases.



▲ **Figure 17–1.3C** Flow-Volume Loop: Normal

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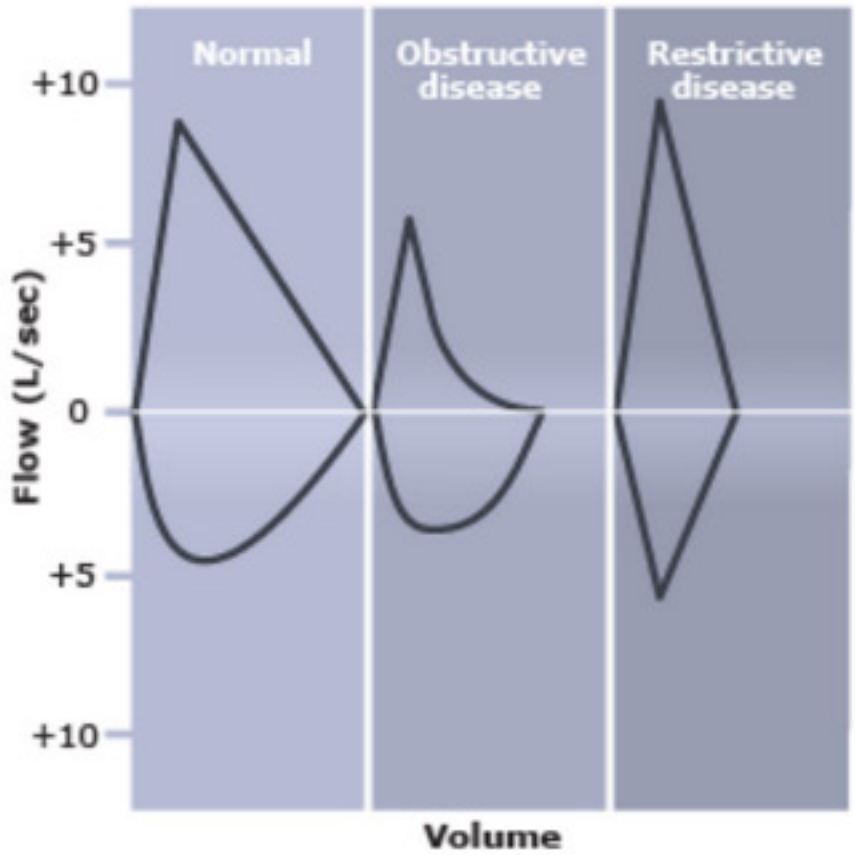

▲ **Figure 17–1.3D** Flow-Volume Loops: Obstructive vs. Restrictive Pattern

Obstructive Disease

FVC ↓

Flow ↓

Scalloped-out portion of descending limb

Restrictive Disease

FVC ↓

Peak flow close to normal

Width of loop noticeably narrower

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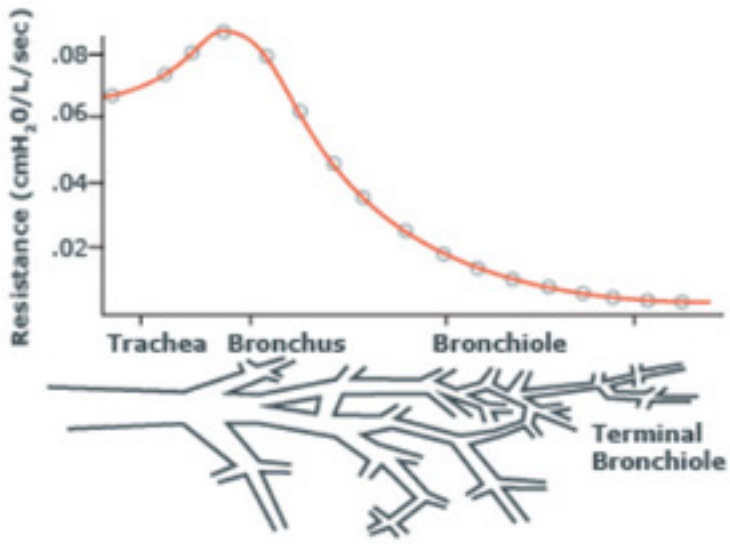
1 Resistance of the Airways

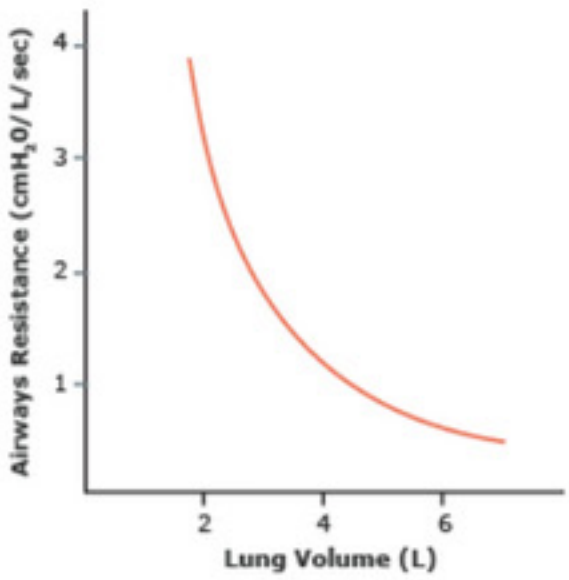
As with the systemic circuit, the respiratory system is a branching tree. Branching produces more tubes in parallel, reducing resistance—but, as the tubes get smaller, an individual tube's resistance increases. Following the pressure drop along the system demonstrates the greatest resistance in the upper airways. More specifically, resistance peaks in the first and second bronchi. Because of the extensive branching of the airways, the bronchioles represent a very low resistance pathway. They are often referred to as a *silent zone*.



▲ **Figure 18–1.0** Resistance Differences Between Upper and Lower Airways

1.1 Effect of Lung Volume

Radial traction by the lung tissue (guy-wire effect) helps to maintain patent airways. In addition, as the lung expands, the radial traction expands the airways and decreases resistance. Breathing at large lung volumes minimizes airway resistance.



▲ **Figure 18–1.1** Effect of Lung Volume on Airway Resistance

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1.2 Effect of Intrapleural Pressure

During forced expiration, the positive intrapleural pressure essentially squeezes the airways, particularly the small airways. Exhaling more forcefully exacerbates the situation, particularly in obstructive diseases. Expiring with pursed lips creates a high resistance point at the end of the system. Pressure rises within the airways, reducing the tendency to collapse.

1.3 Modulation

- Sympathetic β_2 receptors—agonists dilate
  - Albuterol, Salmeterol
- Anticholinergics
  - Ipratropium, Tiotropium
- Inflammation of the airways (asthma, severe COPD)
  - Inhaled or systemic corticosteroids
  - Leukotriene antagonists (montelukast)

  These interventions work over time. Bronchodilators work more quickly.

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2 Ventilation and Dead Space

2.1 Total Ventilation

Total ventilation is the volume of air moved in or out of the respiratory system per minute, usually measured as the volume expired per minute. This is often referred to as *minute ventilation* or *minute volume*.

$V_E = V_T \times f$ V_E = Minute volume (expired)
V_T = Tidal volume
f = Respiratory frequency

Normal resting individual: V_T = 500 mL f = 12/min
V_E = 500 × 12 = 6,000 mL/min

2.2 Dead Space

Dead space represents any air in the respiratory system that is not exchanging oxygen and carbon dioxide with the pulmonary capillary blood. The most important dead space for our purposes is the anatomic dead space.

2.2.1 Anatomic Dead Space

Anatomic Dead Space (ADS) is the air in the conducting airways all the way down to and including the terminal bronchioles. The respiratory bronchioles can be considered a transition region. Air within the alveolar ducts and alveoli should be exchanging O_2 and CO_2, and constitutes a respiratory zone.

The volume of the anatomic dead space in mL can be approximated by the person's weight in pounds. Thus, a 70 kg (154 lb) individual has a dead space of 154 mL (about 150 mL).

2.2.2 Alveolar Dead Space

Alveoli ventilated but without capillary blood flow (see V/Q mismatch).

2.2.3 Physiological Dead Space

Total dead space (anatomic + alveolar).

2.2.4 Dead Space vs. Respiratory Zone Composition

Consider the lung as a simple balloon model. The neck of the balloon is the anatomic dead space (ADS) and the remainder the respiratory zone (RZ).

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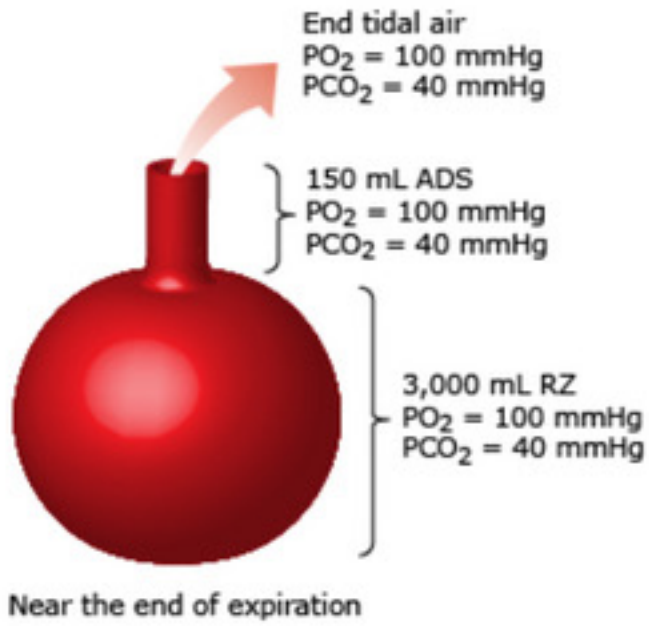
2.3 Situation at the End of Expiration

Ventilation exchanges a small volume compared to the large volume of the respiratory zone, so this region is considered a fairly constant environment. Alveolar PO_2 = 100 mmHg, PCO_2 = 40 mmHg, PN_2 = 573 mmHg, PH_2O = 47 mmHg. Notice that at sea level, the pressures in the alveoli total 760 mmHg. Since at the end of expiration, the dead space is filled with air from the alveoli, their composition will be the same. The air expired in the latter part of expiration also originated from the alveoli (end tidal air). Its composition closely reflects the composition of the alveolar air.

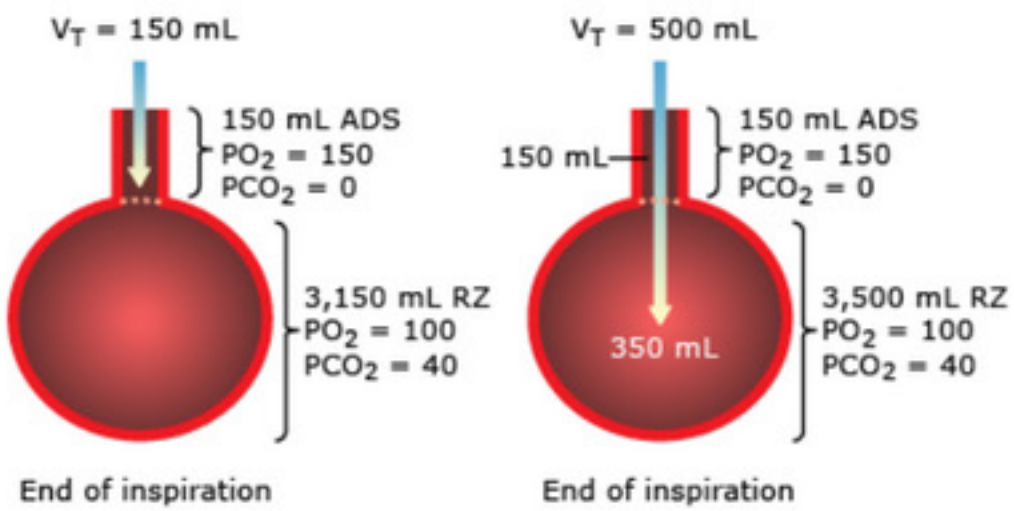


▲ **Figure 18–2.3** Restful Breathing: Near the End of Expiration

2.4 Situation at the End of Inspiration

If the tidal volume was 150 mL, dead space air returns to the respiratory zone, and the dead space fills with room air. However, no room air reaches the respiratory zone. If the tidal volume was 500 mL, 150 mL of the room air remains in the dead space, and the remaining 350 mL is added to the respiratory zone. At the end of inspiration, the dead space is filled with humidified room air (PO_2 = 150 mmHg, PH_2O = 47 mmHg, PCO_2= 0). We assume room air has zero CO_2.

In summary, the first 150 mL of the tidal volume fills the dead space with room air, but no room air reaches the respiratory zone. Every mL above 150 adds to the respiratory zone.



▲ **Figure 18–2.4** Restful Breathing: End of Inspiration; V_T = 150 mL vs. V_T = 500 mL

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2.5 Alveolar Ventilation

Alveolar ventilation is the room air that reaches the respiratory zone per minute. The first 150 mL of the tidal volume fills the dead space and does not contribute to alveolar ventilation.

$V_A = (V_T - V_D) \times f$

V_A = alveolar ventilation
V_T = tidal volume
V_D = dead space
f = respiratory frequency

$= (500 \text{ mL} - 150 \text{ mL}) \times 12 = 4{,}200 \text{ mL/min}$

Note: This is a required calculation for Step 1.

2.5.1 Example: Comparing Total and Alveolar Ventilation

Consider the following individuals. With patient A the normal reference and dead space 150 mL:

Ventilation	V_T	f	Total Ventilation	Alveolar
Patient A	500 mL	10/min	5,000 mL/min	3,500 mL/min
Patient B	600 mL	10/min	6,000 mL/min	4,500 mL/min
Patient C	500 mL	12/min	6,000 mL/min	4,200 mL/min
Patient D	300 mL	18/min	5,400 mL/min	2,700 mL/min
Patient E	600 mL	15/min	9,000 mL/min	6,750 mL/min

Summary Patient B increased depth of breathing at the same rate. Equal increases in total and alveolar ventilation; every additional mL of the tidal volume contributed to alveolar ventilation.

Patient C increased rate at the same depth. Total ventilation increases more than alveolar ventilation. For each additional tidal volume of 500 mL, only 350 mL contributed to alveolar ventilation.

Patient D has rapid, shallow breathing. Total ventilation is above normal, but alveolar ventilation is below normal (hypoventilation).

Patient E has rapid, deep breathing (Kussmaul breathing, diabetic ketoacidosis), alveolar ventilation above normal (hyperventilation).

Conclusion In rapid shallow breathing, the patient appears to be moving a lot of air, but it is not generally hyperventilation, rather, it is usually hypoventilation (restrictive diseases).

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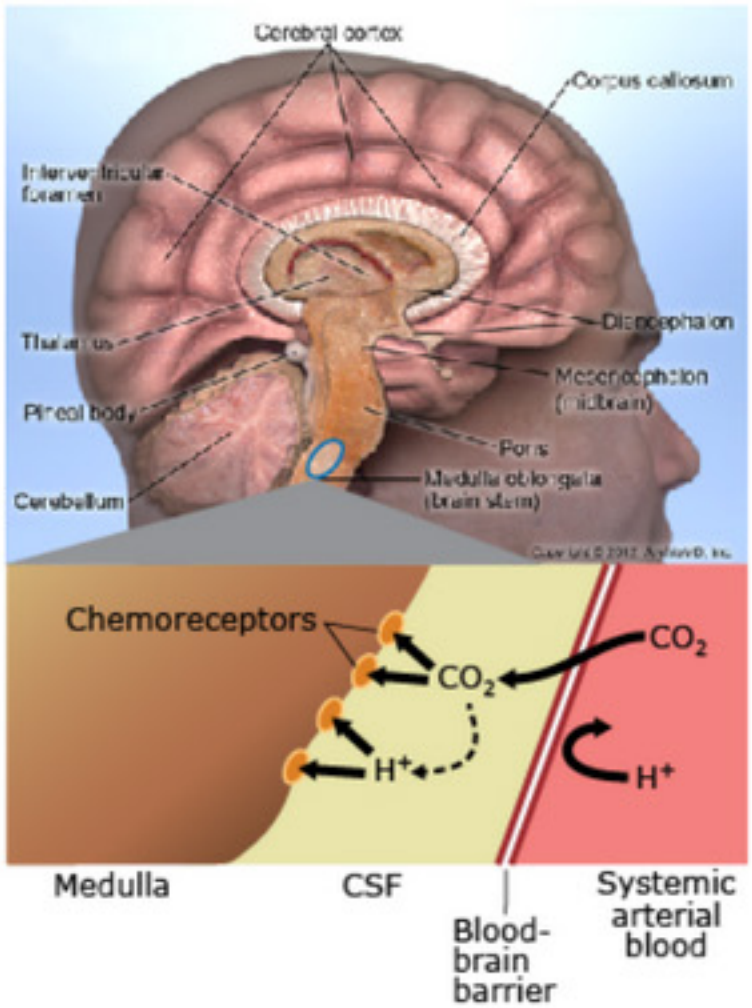
3 Regulation of Alveolar Ventilation

The inherent rhythm for breathing originates within the medulla of the brain stem. Here, the input from the chemoreceptors determines the overall output and the level of alveolar ventilation. The greater the stimulation of the chemoreceptors, the greater the level of alveolar ventilation. The chemoreceptors that respond to pH, PCO_2, and PO_2 are located within the central nervous system and in the periphery.

3.1 Central Chemoreceptors

The central chemoreceptors are located just below the ventrolateral surface of the medulla. Because of their location, they directly monitor the chemical composition of the cerebrospinal fluid. They are stimulated by H^+ ions and also by CO_2, but possibly indirectly through its conversion to H^+.

- Because the blood-brain barrier is permeable to CO_2, systemic arterial CO_2 also stimulates the receptors, but after a short delay. CO_2 must diffuse from the blood to the receptors. The blood-brain barrier is not very permeable to blood H^+. It takes hours for any change in arterial pH to affect the central receptors. Thus, a lactate acidosis following exercise has a minimal central effect on ventilation.
- The central receptors are extremely sensitive and keep the arterial CO_2 within a narrow range. They are the most sensitive receptors affecting alveolar ventilation and represent the main drive for ventilation under normal conditions.



▲ **Figure 18–3.1A** Location of the Central Chemoreceptors

Important Concept

The main drive for ventilation is CO_2 (via H^+) on the central chemoreceptors.

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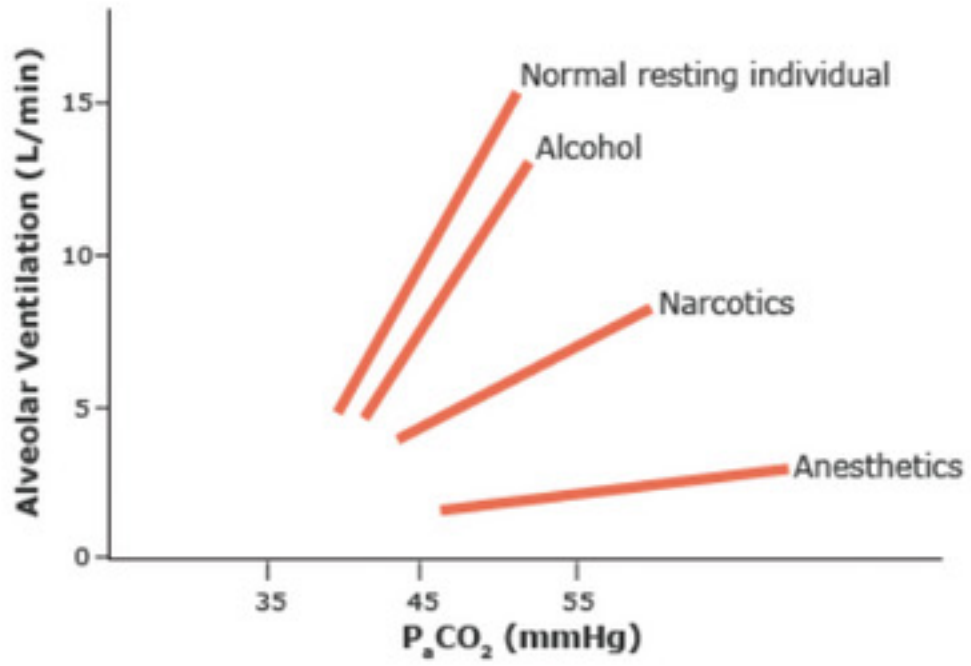
Sensitivity of the receptor/central control center is reduced in a number of situations. Chronic CO_2 retention is thought to directly decrease the sensitivity of the receptors. Other factors are presented below.

The central nervous system does not possess PO_2 receptors. *It is always a distractor on the exam.*



▲ **Figure 18–3.1B** Factors Affecting Sensitivity of Central Chemoreceptors

3.2 Peripheral Chemoreceptors

Found within the carotid and aortic bodies. Carotid bodies are located within the bifurcations of the carotid arteries near the carotid sinus. Their afferent fibers join the glossopharyngeal (IX) nerve. Aortic bodies are located along the aortic arch. Their afferents join the vagus nerve (X). Each structure receives its own blood supply that is extremely high per gram of tissue. Consequently, the receptors are bathed in arterial, not venous blood. The carotid bodies can be considered the most important.

3.2.1 Receptors

- **CO_2/H^+:** These receptors are not as sensitive as the central receptors, but they respond more rapidly to changes in the arterial CO_2. They contribute about 30% of the normal drive for ventilation.
- **PO_2:** The PO_2 of the blood is created by dissolved oxygen in the plasma. Thus, they respond to plasma oxygen not oxygen bound to hemoglobin or oxygen content. There is no receptor to monitor oxyhemoglobin. At normal or above normal arterial PO_2 there is little stimulation of the PO_2 receptors. However, they are strongly stimulated by a decrease (PO_2,< 75 mmHg). CO_2 retention increases the sensitivity to a PO_2 decrease, and there is no adaptation of PO_2 receptors with time.

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3.2.2 Summary

- Under normal conditions, the total drive for ventilation is CO_2 mainly via the central receptors.
- Elimination of the peripheral input causes a modest decrease in alveolar ventilation.
- Under normal conditions, there is no PO_2 drive for ventilation.
- With a significant drop in arterial PO_2, the peripheral receptors are strongly stimulated and constitute the main drive for ventilation.

3.3 Chronic Hypoventilation (COPD)

Maintains elevated levels of CO_2 and a decreased PO_2 in systemic arterial blood. The assumption is that the elevated CO_2 reduces the sensitivity of the CO_2 receptors, and the main drive for ventilation can then be the depressed arterial PO_2 acting on the peripheral chemoreceptors.

3.4 Mechanoreceptors

- **Irritant receptors:** Found in the epithelium along the conducting airways. Respond to inhaled dust, noxious gases, and cigarette smoke. Cause bronchial constriction.
- **J receptors:** Originate in the alveolar walls and are stimulated with pulmonary edema and inflammation. May cause a sensation of dyspnea.
- The **Hering-Breuer reflex** is of no significance under normal conditions.

Important Concept

COPD: Supplemental oxygen administered above a critical level in a COPD patient decreases the hypoxic drive for breathing, further depressing ventilation and elevating CO_2. The cardinal rule is to never give these patients near 100% oxygen.

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4 Muscles of Respiration

4.1 Inspiration

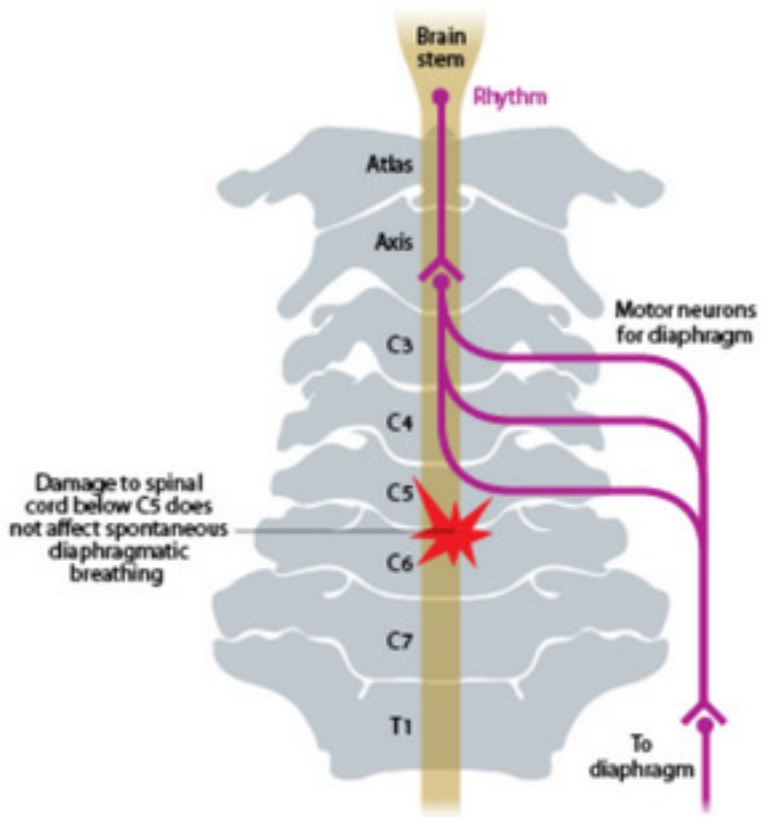
- **Diaphragm:** The main muscle of inspiration. Shaped as a dome, it is flattened by contraction, which intensifies negative intrapleural pressure. Motor neurons arise from the cervical region of the spinal cord (C3, 4, 5).
- **Intercostal muscles:** Contraction raises the rib cage and increases the anteroposterior dimension of the chest wall. Motor neurons arise from the thoracic region.

4.2 Expiration

- Under resting conditions, achieved by simply a relaxation of the muscles of inspiration.
- Active expiration (and coughing) is produced by the contraction of the abdominal muscles. The accompanying increased pressure in the abdominal cavity forces the diaphragm in a rapid central direction.
- All the abdominal muscles contribute: Rectus abdominal, obliques, and transverse abdominal.
- The obliques are considered the main muscles of expiration and cough.

4.2.1 Spinal Cord Injury

Spontaneous breathing requires an intact functioning central respiratory center and output to the diaphragm. Upper-level tetraplegic (C1, 2) complete transection does not allow for diaphragmatic breathing and requires permanent mechanical support. Transection below C5 maintains diaphragmatic breathing in lower-level tetraplegics and all paraplegics.



▲ **Figure 18–4.2** Nervous Innervation of the Diaphragm

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5 Abnormal Breathing Patterns

5.1 Cheyne-Stokes Breathing

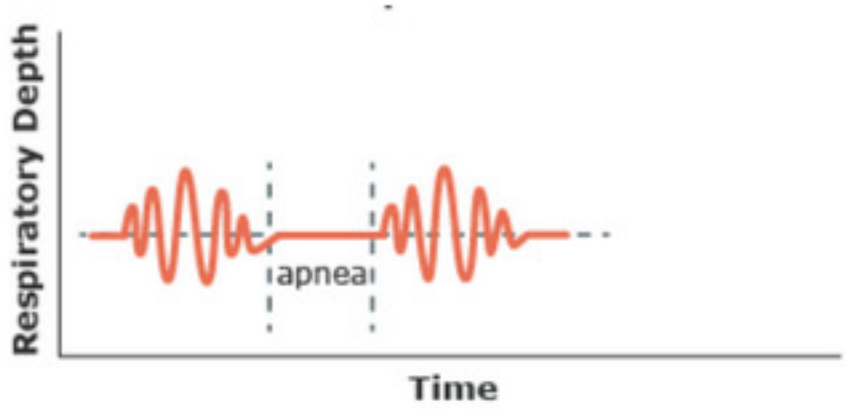
Period of apnea followed by gradually increasing, then decreasing tidal volumes until next apnea. Abnormal breathing pattern in head trauma and increased intracranial pressure. It also appears at high altitude, during sleep, and in normal infants.

5.2 Biot Breathing

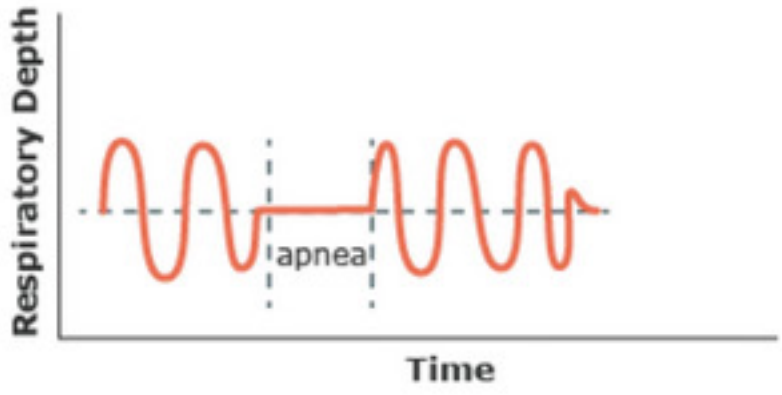
Abnormal breathing pattern characterized with short periods of regular rhythmic breathing separated with irregular periods of apnea. When the breathing phase becomes irregular, it is referred to as *ataxic* breathing. Caused by damage or pressure on the medulla due to trauma or stroke.

5.3 Apneustic Breathing

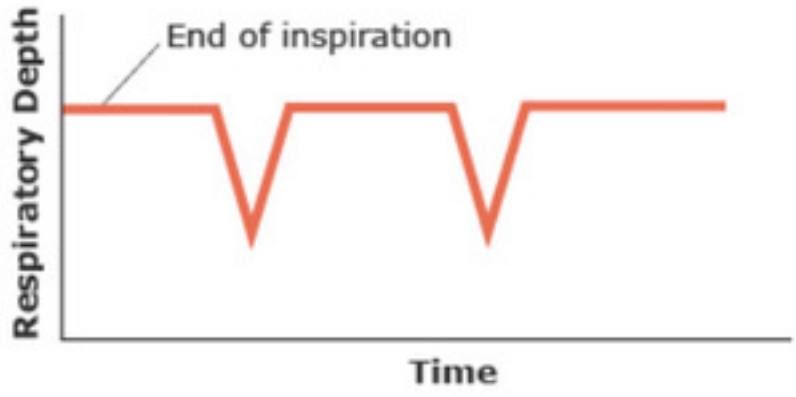
Abnormal pattern with deep, gasping inspirations held for a few seconds separated by short periods of expiration. Caused by damage to the pons or upper medulla disrupting the normal pneumotaxic center-medullary interactions. Lesion usually found in the caudal pons.



▲ **Figure 18–5.3A** Cheyne-Stokes Breathing



▲ **Figure 18–5.3B** Biot Breathing



▲ **Figure 18–5.3C** Apneustic Breathing

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1 Forces on the Lung System

In quiet, restful breathing, there are two opposing forces to consider: elastic recoil of the lung and pleural pressure.

1.1 Elastic Recoil of the Lung

Created by stretching the elastic and collagen fibers of the lung tissue and the surface tension forces trying to collapse the alveoli.

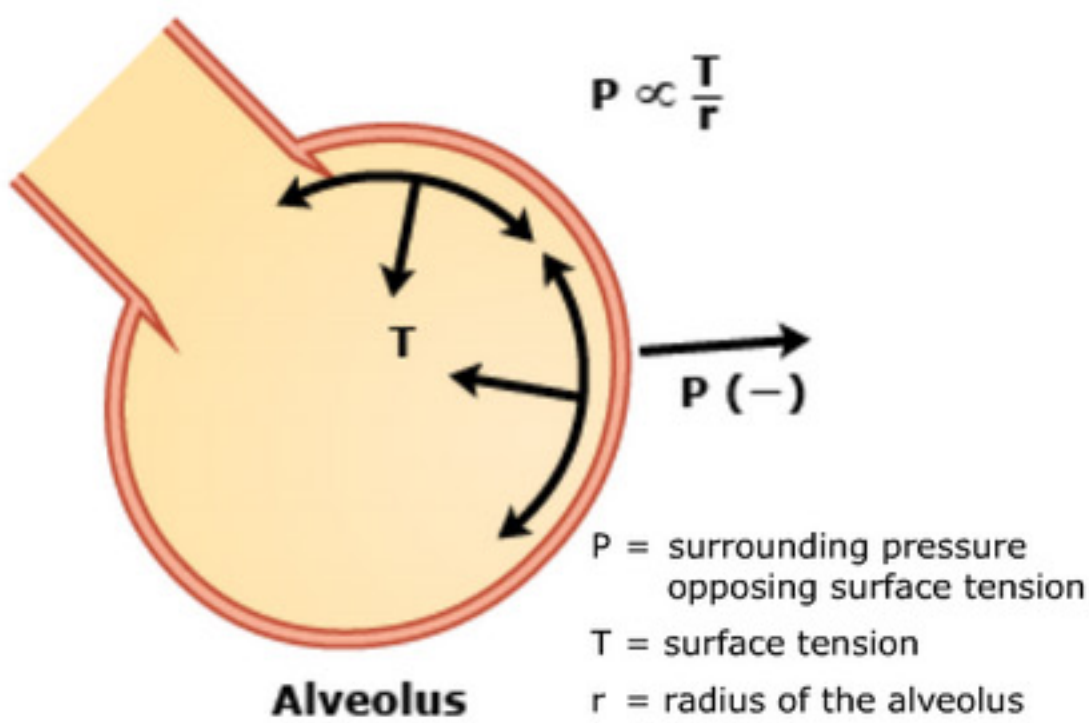
Elastic recoil always acts inward, trying to collapse the lung.

The magnitude of the force is directly proportional to lung size.

Expansion increases the force of recoil, and the reverse decreases the force of recoil.

1.1.1 The Two Components of Lung Recoil

1. The collagen and elastic fibers, and the pattern with which they are interwoven within the lung tissue. The tissue elastic forces represent about one-third of the total recoil.
2. At the air-liquid interface within the alveoli, the attractive force between the water molecules creates the surface tension forces. These forces are always directed inward, trying to collapse the alveoli. The relationship between this force and alveolar radius is given by the law of LaPlace.



▲ **Figure 19–1.1A** LaPlace Relationship Applied to an Alveolus

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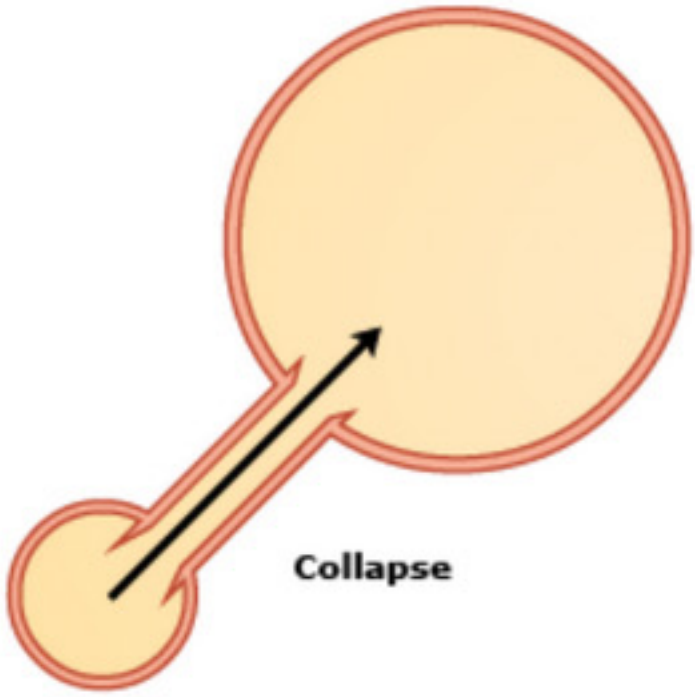

▲ **Figure 19–1.1B** A Consequence of the LaPlace Relationship

Consider a small bubble and a larger bubble with the same surface tension. The pressure in the small bubble is higher than in the large bubble. So, if they were suddenly connected, the smaller would collapse and blow up the larger. In the lung, the situation is not identical, but the Laplace relationship demonstrates that small alveoli are very unstable. They have a strong tendency to collapse, creating regions of atelectasis. Atelectasis is an example of a pulmonary shunt; there is blood flow with no ventilation. It takes a strong inspiratory effort to reinflate these alveoli.

1.2 Pleural Pressure

- Pressure in the thin film of fluid separating the lung from the chest wall.
- At FRC, in the neutral or equilibrium state, recoil forces act to collapse the lung, and the rib cage attempts to spring outward. The two opposing forces create a negative pleural pressure (−5 cmH_2O).
- Negative pleural pressure acts to expand the lung.
- Positive intrapleural pressure (contraction of abdominal muscles) acts to collapse the lung.
- If the negative pleural pressure is the stronger force, the lung expands.
- If recoil is the stronger force, the lung gets smaller.

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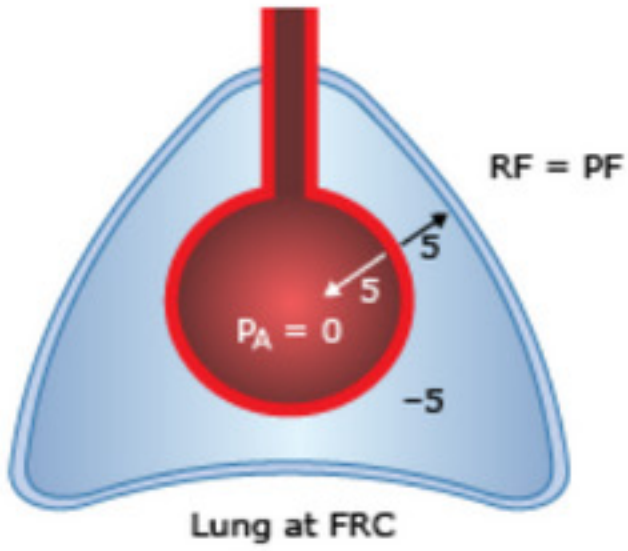
2 The Normal Restful Cycle

2.1 Situation at FRC

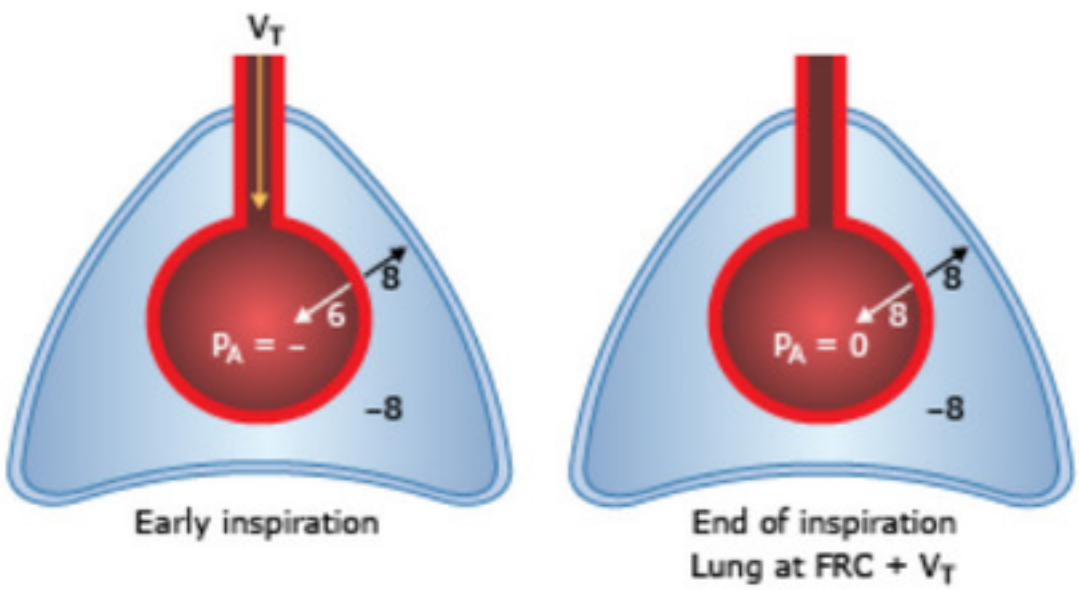
- **Pleural Pressure:** −5 cmH_2O due to equal but opposite forces.
  Glottis open, no air flowing, alveolar pressure (P_A) = 0.
  Pleural force = PF Recoil force = RF



▲ **Figure 19–2.1** Mechanics of Restful Breathing: At FRC

2.2 Inspiration

- Contraction of diaphragm, pleural pressure becomes more negative, −5 to −8 (PF ↑)
- Lung expands (PF > RF) until RF increases to equal PF
- Expansion of the alveoli (P_A = −), air flows into the lung
- Tidal volume drawn into the lung raises P_A back to zero



▲ **Figure 19–2.2** Mechanics of Restful Breathing: Inspiration

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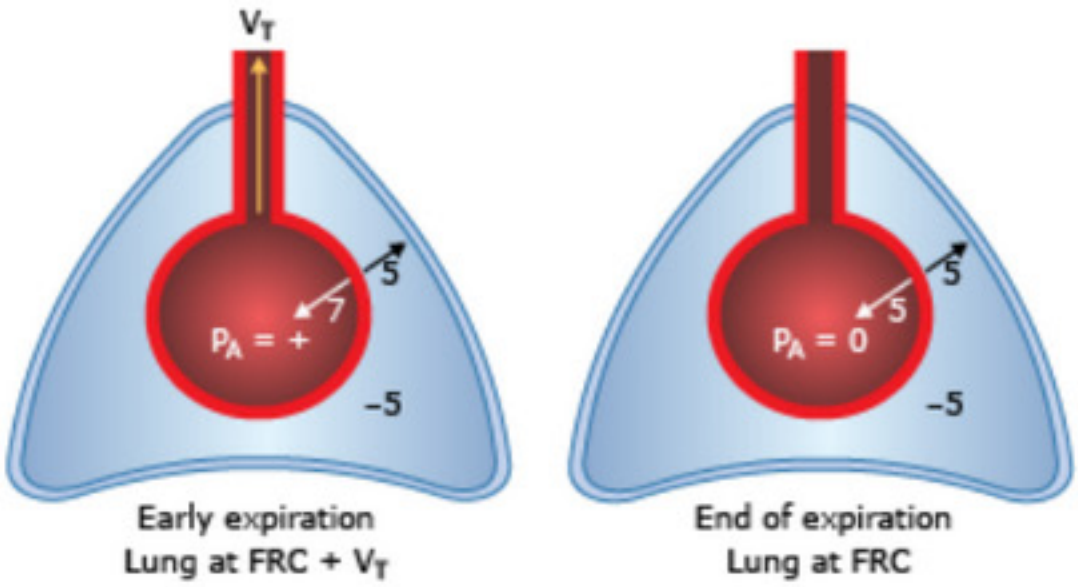
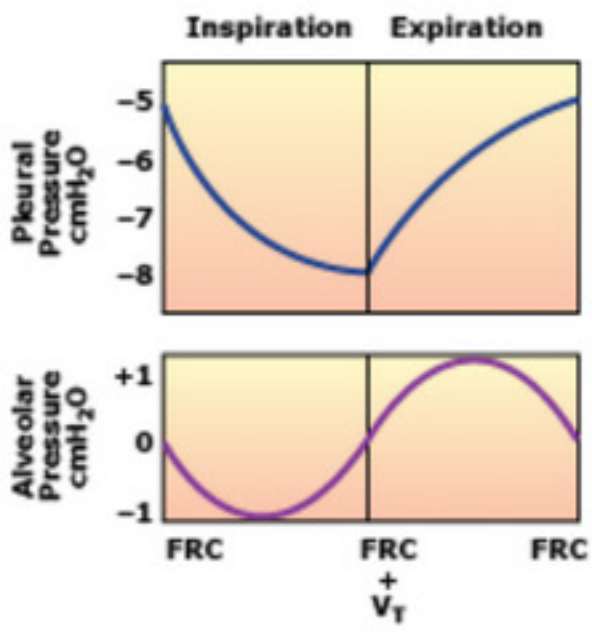
2.3 Expiration

- Relaxation of diaphragm, pleural pressure more positive, −8 to −5 (PF ↓)
- Lung gets smaller (RF > PF) until RF decreases to equal PF
- Compression of the alveoli (P_A = +), air flows out of the lung
- Tidal volume expelled lowers P_A back to zero



▲ **Figure 19–2.3A** Mechanics of Restful Breathing: Expiration

Changes in Pleural and Alveolar Pressure During the Restful Cycle



▲ **Figure 19–2.3B** Changes in Pleural and Alveolar Pressure During the Restful Cycle

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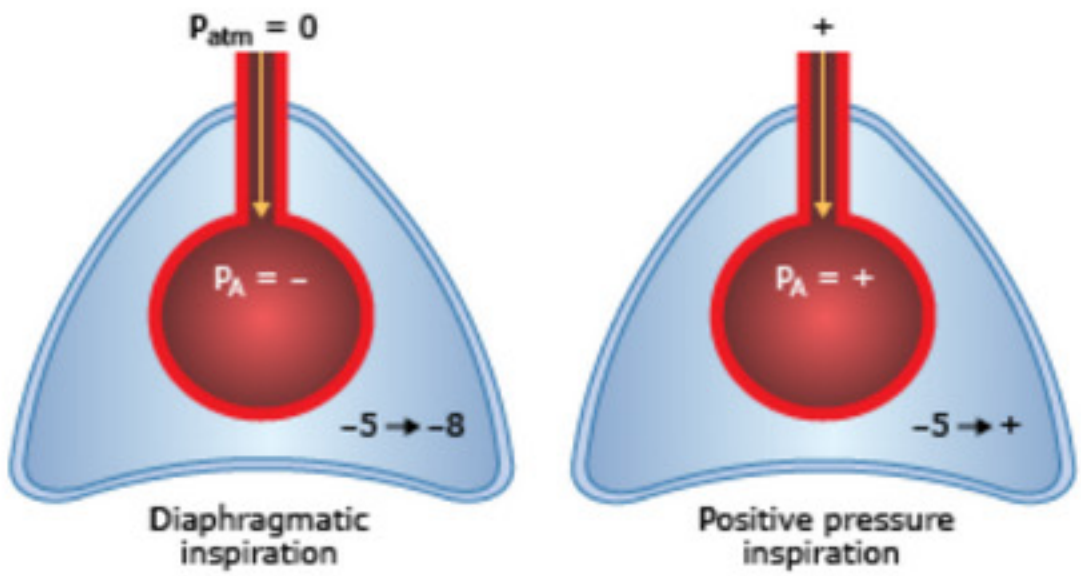
3 Positive Pressure Ventilation

With diaphragmatic inspiration, pleural pressure becomes more negative, creating a negative alveolar pressure that pulls in the tidal volume.

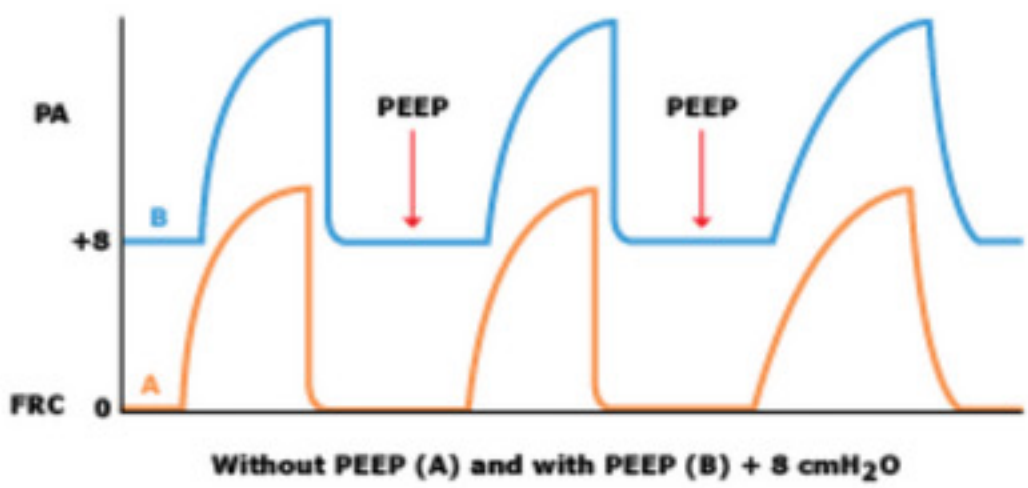
With positive pressure ventilation, the tidal volume is pumped into the lungs, as in blowing up a balloon. During inspiration, alveolar pressure is becoming more and more positive. It is at its most positive at the end of inspiration.

Note: On a positive pressure ventilator, tidal volume must be sized appropriately. If tidal volume is inappropriately large, alveolar pressure is excessive at the end of inspiration. This can cause a spontaneous pneumothorax, often at the lung apex.



▲ **Figure 19–3.0A** Mechanics of Inspiration: Diaphragmatic vs. Positive Pressure Ventilator

As shown on the following graph, at FRC alveolar pressure is zero. Pumping air into the lung creates a positive pressure in the alveoli. It is at its most positive at the end of inspiration. The trachea is then connected to room air, the positive alveolar pressure pushes out the tidal volume, and at FRC, alveolar pressure is again zero (situation A). In many cases, expiration is terminated before FRC (situation B). The termination pressure is referred to as PEEP (*positive end-expiratory pressure*). If cycling now begins at PEEP, the alveoli cycle at a larger size.



▲ **Figure 19–3.0B** Positive Pressure Breathing With and Without PEEP

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PEEP has two advantages:

1. First, larger alveoli are more stable. They have less tendency to collapse, creating regions of atelectasis, equivalent to shunted regions in the lung.
2. Second, cycling at larger alveoli creates a more uniform ventilation among lung regions. This makes supplemental oxygen more effective.

   One negative of applying a positive inspiratory pressure is that pleural pressure becomes more positive with inspiration. This can decrease venous return into the right heart and cardiac output. The effect is exaggerated with PEEP.

On a positive pressure ventilator, ventilation is set based on end-tidal CO_2. If PO_2 is a problem, supplemental oxygen is added.

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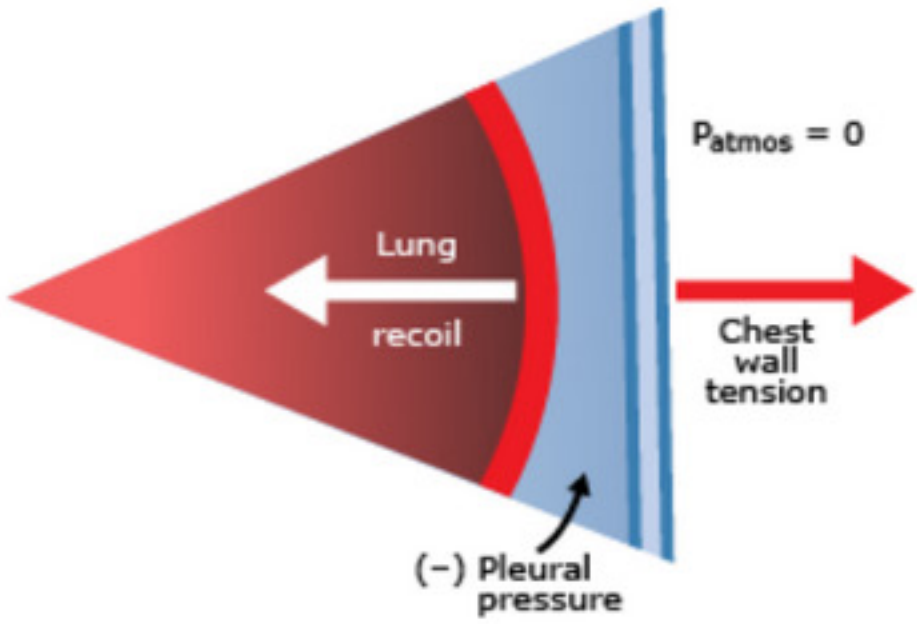
4 Pneumothorax

Due to the elastic recoil of the lung and chest wall tension, pleural pressure is negative at FRC.



▲ **Figure 19–4.0** Negative Pleural Pressure Created by Opposing Forces of Lung Recoil and Chest Wall Tension

4.1 Results of Pneumothorax

- Air flows from the higher atmospheric pressure into the pleural space.
- The air pocket formed in the pleural space disconnects the lung from the chest wall.
- The lung collapses due to the unopposed force of recoil, and the chest wall expands.
- The collapsed lung region acts as a pulmonary shunt.

4.2 Two Types of Pneumothorax

- **Simple pneumothorax:** Air can flow in and out of the pleural space with the respiratory cycle.
- **Tension pneumothorax:** Tissue surrounding the chest opening acts as a one-way valve. Air flows in during inspiration but not out during expiration.
- There can also be a spontaneous pneumothorax. This often occurs with positive pressure ventilation at the lung apex. A spontaneous pneumothorax often becomes a tension pneumothorax.

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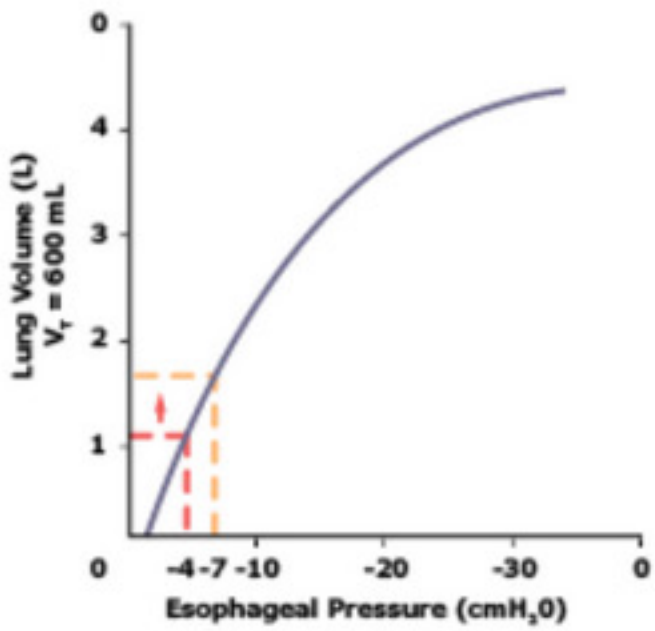
5 Lung Compliance

Lung compliance is defined in the following equation. However, calculations are based on inspiration rather than expiration.

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

A spirometer measures the change in *lung volume*, and an esophageal balloon-tipped catheter measures the *change in pleural pressure* during the respiratory cycle. The absolute values at the catheter tip are slightly different than true pleural pressure.



▲ **Figure 19–5.0** Lung Inflation Curve

$$V_T = 600 \text{ mL} \quad \text{Compliance} = \frac{600 \text{ mL}}{3 \text{ cmH}_2\text{O}} = 200 \text{ mL/cmH}_2\text{O}$$

FRC = −4 cmH_2O

FRC + V_T = −7 cmH_2O

Thus if pleural pressure:

−4 cmH_2O → −5 cmH_2O inspired V_T = 200 mL

−6 cmH_2O → −4 cmH_2O expired V_T = 400 mL

For every 1 cmH_2O change in pleural pressure, 200 mL of air flows.

Increased compliance = Larger volume flows per change in pleural pressure.

Decreased compliance = Smaller volume flows per change in pleural pressure.

The $\Delta V/\Delta P$ is also the slope of the inflation curve. The greater the slope (steeper the line), the more compliant the lung. At rest, the individual operates on the steep part of the curve (the most compliant part). As one moves toward TLC, the curve flattens, and the lung becomes stiffer.

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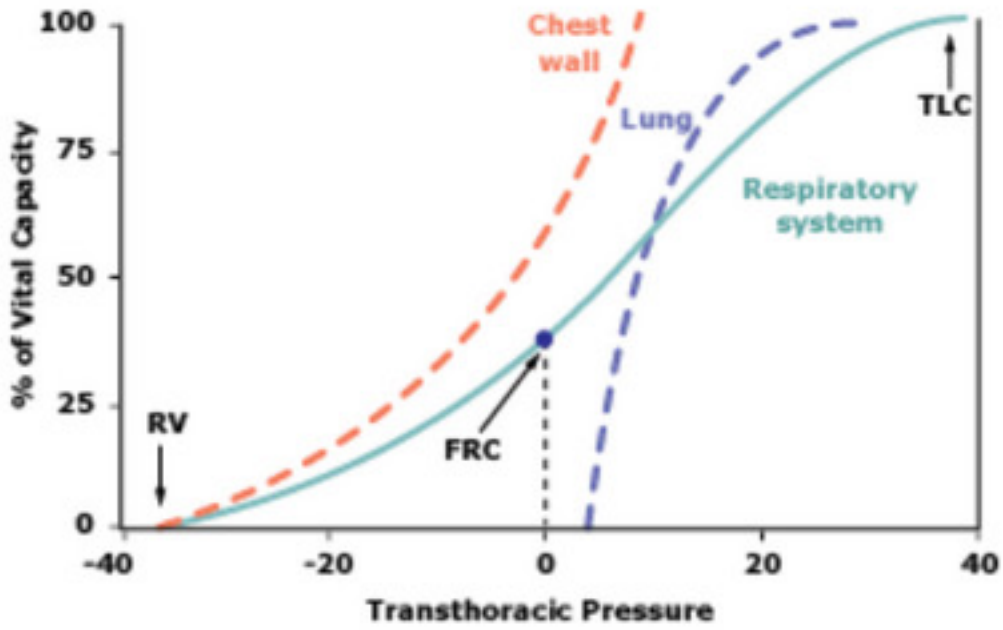
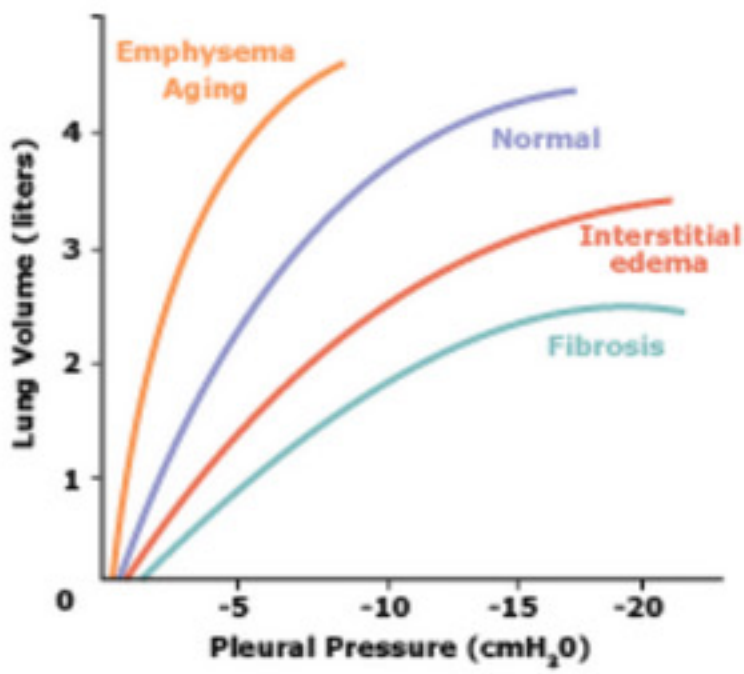
5.1 Inflation Curves, Respiratory System

The following figure shows inflation curves for the lung, chest wall, and the entire respiratory system. The respiratory system curve is the sum of the lung and chest wall alone. A special maneuver is performed to generate these curves. A transthoracic pressure of zero represents FRC for the entire respiratory system.



▲ **Figure 19–5.1** Inflation Curves: Lung, Chestwall, and the Entire Repiratory System

5.2 Inflation Curves, Clinical Shift



▲ **Figure 19–5.2** Lung Inflation Curves: Obstructive vs. Restrictive Pattern

- Emphysema, often caused by smoking, results in destruction of the alveolar septa and capillaries. This reduces the elastic recoil, increasing compliance. Filling the alveoli with saline also decreases the elastic recoil by eliminating surface tension forces in the alveoli. Airway resistance per se is not a factor in compliance.
- Fibrosis has increased collagen fiber deposition, which increases the tissue component of elastic recoil.

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5.3 Surfactant and Surface Tension

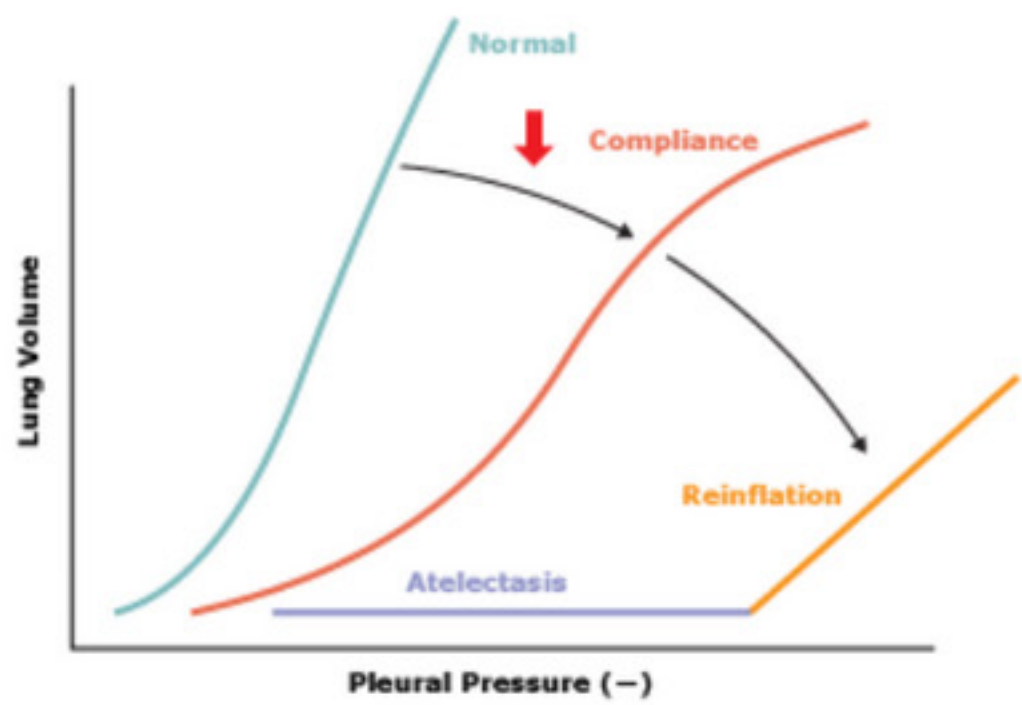
Without the presence of surfactant, surface tension forces in the alveoli would be excessive to the point that lung inflation would not be possible. Surfactant is a surface active agent that reduces surface tension forces. It is produced by type II alveolar cells.

Surfactant has three important properties:

- Surfactant lowers the surface tension forces in the alveoli. In this way, surfactant lowers recoil and increases the compliance of the lung.
- Surfactant produces a greater decrease in surface tension in smaller alveoli. Thus, it decreases their tendency to collapse.
- Since surfactant reduces recoil, pleural pressures are closer to atmospheric. A pleural pressure of −5 cmH_2O is not transmitted to the pulmonary capillaries. It is not a force promoting pulmonary edema.

5.4 Respiratory Distress Syndrome (ARDS, Acute Lung Injury)

The infant form is a true deficiency of surfactant. ARDS represents an injury to the alveolar membrane. As such, interstitial proteins enter the alveolus and carry water with them. In addition, protein in the alveolus antagonizes the effects of surfactant. Causes can include gastric aspirations and sepsis.



▲ **Figure 19–5.4** Lung Inflation Curves: Respiratory Distress Syndrome

- Since the curve shifts to the right, the lung becomes stiffer, and compliance decreases. This greatly increases the work of breathing. Also, a more negative pressure is required to maintain a given lung volume.
- Lung regions collapse, creating regions of atelectasis. This creates pulmonary shunting and hypoxemia. Reinflation requires exceptionally negative pleural pressures.
- Alveolar injury and the very negative pleural pressure create pulmonary edema.

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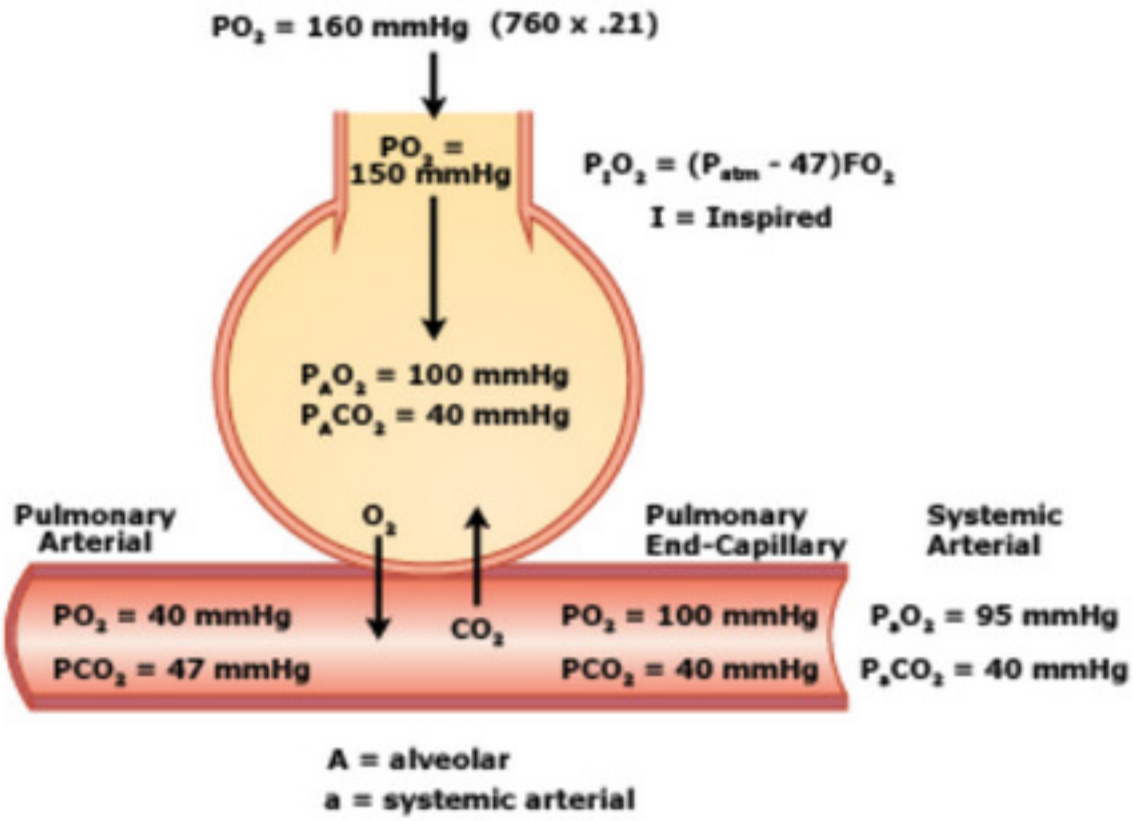
1 Introduction

P_{atm} = 760 mmHg (sea level)
PN_2 = 0.79 × 760 = 600 mmHg
PO_2 = 0.21 × 760 = 160 mmHg

Inspired air is warmed (37°C) and humidified. PH_2O = 47 mmHg



▲ **Figure 20–1.0** PO_2 and PCO_2 Within Pulmonary Compartments

The alveolar compartment and the pulmonary blood equilibrate and thus pulmonary end-capillary values equal the alveolar values. There is a slight decrease in PO_2 between the pulmonary end-capillary blood and systemic arterial because of the natural shunting of blood through the lungs.

Overall for PO_2 and PCO_2: End-tidal air = alveolar = pulmonary end-capillary = systemic arterial.

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2 Factors Determining Alveolar PCO_2

The following relationship states that only two variables affect alveolar PCO_2. If the metabolic rate is constant, the only factor affecting alveolar CO_2 is alveolar ventilation.

There is an inverse relationship between alveolar PCO_2 and alveolar ventilation.

This is one of the most important relationships in pulmonary physiology.

$$P_ACO_2 \propto \frac{\textit{Metabolic Rate}}{\textit{Alveolar Ventilation}}$$

P_ACO_2 = 40 mmHg (35 – 45)

Ventilation ↑, then P_ACO_2 ↓

If the end-tidal air has a PCO_2 < 35 mmHg, by definition the individual is *hyperventilating*.

If ventilation 2×, PCO_2 ½ 40 mmHg → 20 mmHg.

Ventilation ↓, P_ACO_2 ↑

If the end-tidal air has a PCO_2 > 45 mmHg, the individual is *hypoventilating*.

If ventilation ½ PCO_2 2× 40 mmHg → 80 mmHg.

Now assume ventilation stays constant.

Metabolism ↑, P_ACO_2 ↑

If metabolism 2× ,P_ACO_2 2× 40 mmHg → 80 mmHg.

During exercise, as the metabolic rate increases, ventilation must have an equivalent increase to maintain P_ACO_2 in the normal range. As long as the end-tidal PCO_2 is in the normal range, the individual is not hyper- or hypoventilating.

The same reasoning holds if body metabolism decreases due to hypothermia.

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3 Factors Determining Alveolar PO_2

The following is the alveolar gas equation, which describes the three important factors that affect P_AO_2. A calculation may be required for Step 1.

$$P_AO_2 = (P_{atm} - 47)F_IO_2 - \frac{P_ACO_2}{R}$$

1. P_{atm} = atmospheric pressure — 760 mmHg at sea level

Hyperbaric chamber at 2× atm	1520 mmHg	(PO_2 = 320 mmHg)
High altitude at ½ atm	380 mmHg	(PO_2 = 76 mmHg)

At high altitude, we still breathe 21% oxygen, but at a low PO_2. Therefore, because we are continuously breathing low-pressure oxygen, alveolar PO_2 is permanently low. High altitude causes *hypoxemia*.

2. F_IO_2 = the fractional concentration of oxygen in the inspired air normally 0.21. If a patient is given supplemental oxygen alveolar PO_2 always rises. The oxygen is replacing the nitrogen in the inspired air.

3. P_ACO_2 = this is always subtracted from the P_IO_2.

Therefore: If $P_ACO_2 \uparrow$, $P_AO_2 \downarrow$. If $P_ACO_2 \downarrow$, $P_AO_2 \uparrow$.

If the respiratory exchange ratio is 1.0, they change the same amount in mmHg—in opposite directions.

Hypoventilation: If P_ACO_2 = 50 mmHg (↑ 10 mmHg), then $P_AO_2 \downarrow$ by 10 mmHg (100 to 90 mmHg) hypoventilation causes hypoxemia.

Hyperventilation: If P_ACO_2 = 30 mmHg (↓ 10 mmHg), then $P_AO_2 \uparrow$ by 10 mmHg (100 to 110 mmHg).

$$R = \text{respiratory exchange ratio} = \frac{CO_2 \text{ produced}}{O_2 \text{ consumed}} \quad \text{Normally} = 0.8$$

Note: Use R = 1.0 only on Step 1. Clinical calculations use 0.8.

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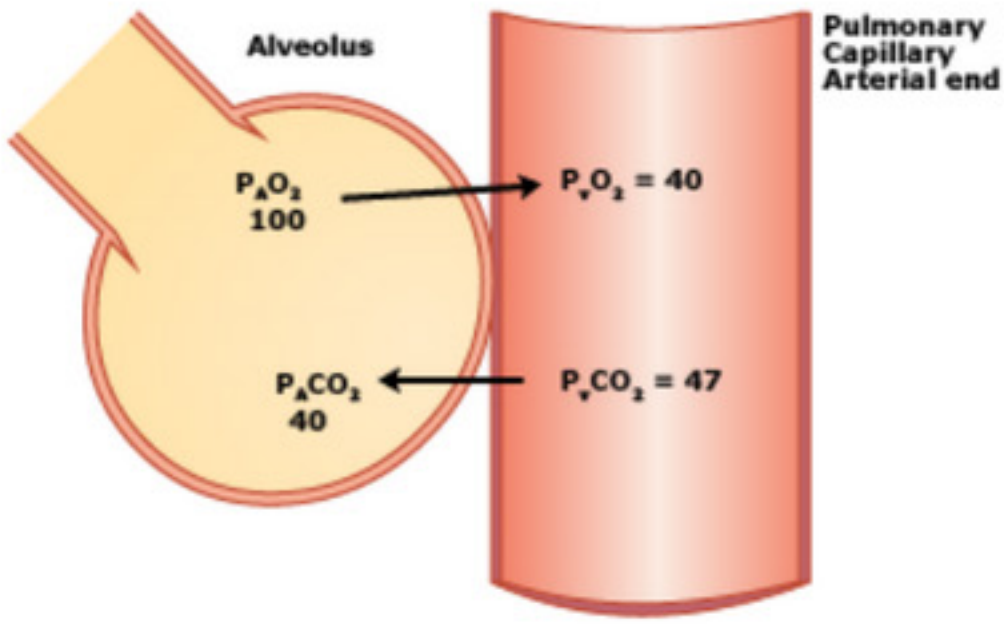
4 Fick Law of Diffusion

The factors that affect the diffusion rate of oxygen and carbon dioxide across lung membranes are the same for any other substance across any membrane system.

Consider the situation as blood enters the pulmonary capillary. Diffusion is passive and depends on a gradient that is, at a maximum, at the beginning of the capillary. Thus, net diffusion is at a maximum at the capillary entrance and decreases downstream as the gradient diminishes.



▲ **Figure 20–4.0** Oxygen and Carbon Dioxide Diffusion Across Lung Membranes

$$\dot{V}_{gas} = \frac{A}{T} \times D \times (P_1 - P_2) \quad \dot{V}_{gas} = \textbf{rate of diffusion}$$

This equation states that there are two structural factors of the membrane and two gas factors that affect the rate of diffusion.

4.1 Structural Factors

It is not possible to quantitate the two structural factors; we can only draw conclusions concerning changes.

A = the total surface area available for diffusion.

↓ = emphysema, complete blockage of an airway, removing lung lobe

↑ = exercise

T = total thickness of the membrane system.

↑ = fibrosis, interstitial and alveolar edema, other restrictive diseases

↓ = slightly during exercise

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4.2 Gas Factors

Each gas has a diffusion constant (D). Although molecular weight is involved, the only clinically relevant feature is solubility. Both oxygen and carbon dioxide are as soluble in the membrane as they are in water. Then, the more soluble the gas is in water, the faster it diffuses across the membrane. CO_2 is 20 times more soluble than O_2. As such, CO_2 always diffuses faster than O_2. Most other clinically relevant gases have a solubility that approximates O_2 rather than CO_2. This includes carbon monoxide (CO).

The partial pressure gradient across the membrane can be considered the net force driving diffusion ($P_1 - P_2$).

Note: These gradients apply to the beginning of the capillary:

O_2 100 − 40 = 60 mmHg

CO_2 47 − 40 = 7 mmHg

Important Clinical Point:

A structural problem decreases the rate of O_2 diffusion. As pointed out previously, supplemental O_2 always raises the P_AO_2. This also means it raises the gradient and accelerates the rate of O_2 diffusion from the alveolus to the capillary blood.

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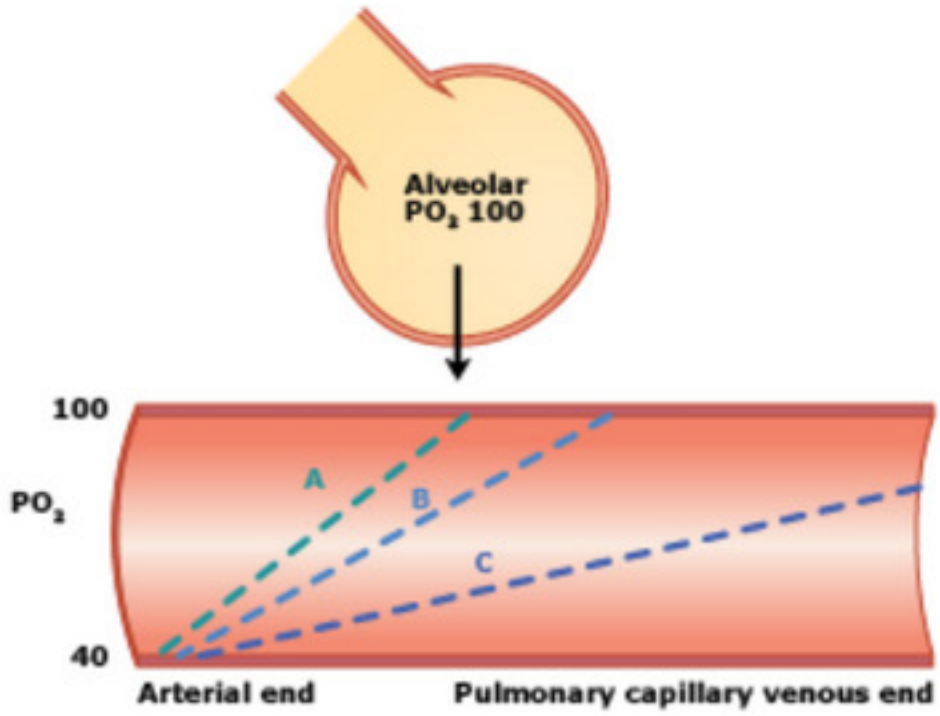
5 Diffusion Capacity DLco

5.1 Perfusion-Limited vs. Diffusion-Limited



▲ **Figure 20–5.1** Perfusion vs. Diffusion-Limited Situation

Situation A: The normal resting individual. Rapid diffusion of O_2 and equilibration between the alveolar compartment and capillary blood about one-third through the capillary. Increasing the rate of diffusion causes earlier equilibration, but O_2 content of the blood leaving the capillary is the same. The delivery of O_2 to the systemic tissues depends only on the rate of perfusion (cardiac output). A *perfusion-limited* situation, with equilibrium between the two compartments.

Situation B: Mild diffusion impairment (structural problem such as ↓ surface area and/or ↑ membrane thickness). Rate of diffusion reduced but still equilibrium established. A "perfusion-limited" situation.

Situation C: Severe diffusion impairment. Equilibrium not obtained. If the rate of O_2 diffusion increased, the O_2 content of the blood leaving the capillary would increase. A "diffusion-limited" situation with no equilibrium between the two compartments.

Note: In hypoventilation, alveolar PO_2 is depressed, and the pulmonary end-capillary blood PO_2 is depressed. But they are the same, and it is still a perfusion-limited situation.

5.2 Carbon Monoxide: Always a Diffusion-Limited Situation

When carbon monoxide diffuses across the alveolar membranes, it attaches to hemoglobin. Almost none dissolves in the plasma, so its partial pressure in the blood can be considered zero. Its gradient across the membrane is the alveolar P_{CO}. Because the partial pressures do not equilibrate across the membrane system, it is always in a diffusion-limited situation.

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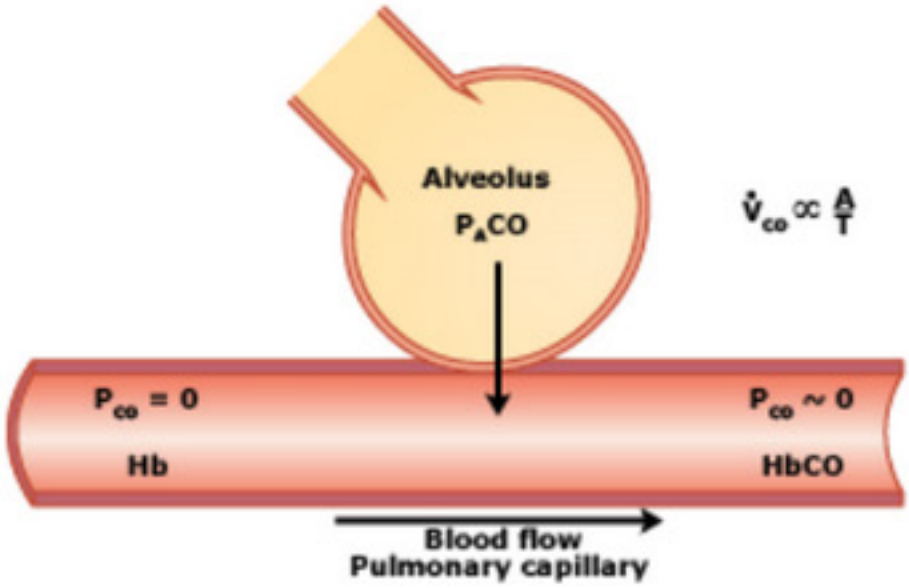
$$\dot{V}_{gas} = \frac{A}{T} \times D \times (P_1 - P_2)$$

$$\dot{V}_{CO} = \frac{A}{T} \times D \times (P_A CO)$$



▲ **Figure 20–5.2** Carbon Monoxide: Always a Diffusion-Limited Situation

If the $P_A CO$ is 1 mmHg in a healthy young individual, the measured uptake is 25 mL/min.

DL_{CO} = Uptake of CO in mL/min/mmHg. It is an index of the lung's structural features (membrane surface area and thickness). With a structural problem, the rate of uptake decreases progressively and correlates with the severity of the disease state.

▼ **Table 20–5.2** Factors Affecting DL_{co}

DL_{co} Decreased	
Alveolar destruction	emphysema
Less perfused alveoli	pulmonary embolism
Thick membrane for diffusions	pulmonary fibrosis
	pulmonary edema
Low cardiac output	heart failure, volume depletion
Low hemoglobin	anemia
DL_{co} Increased	
Exercise	increased cardiac output, increased surface area
Polycythemia	increased hemoglobin
Alveolar hemorrhage	hemoglobin depot
Summary: DL_{co} reflects diffusion out of the lungs and into RBCs.	

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1 Oxygen Transport

1.1 Introduction

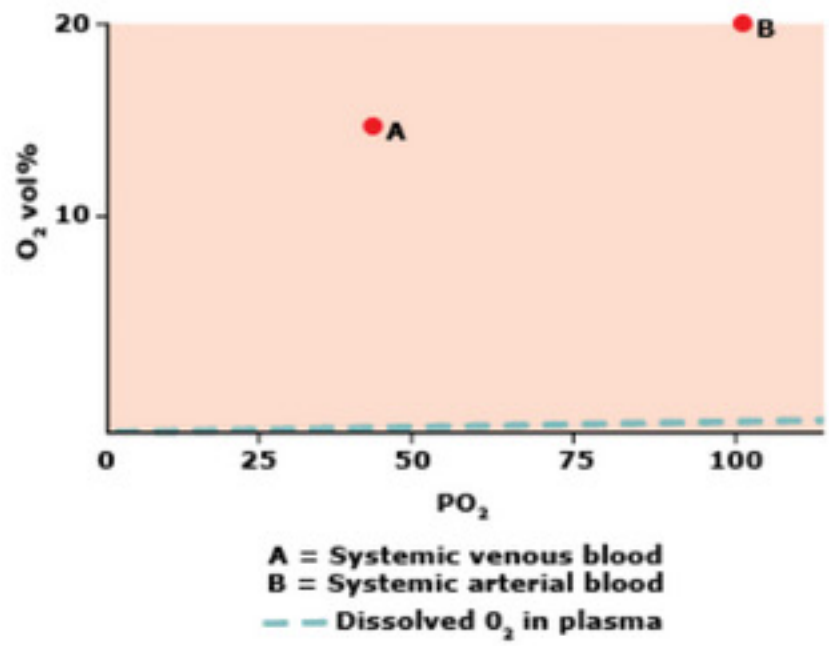
The *concentration* of blood oxygen is usually referred to as blood oxygen *content*. In the systemic arterial blood, it varies with hematocrit, but a value of 20 volumes percent (vol %), (20 mL oxygen/100 mL blood) is a normal value. The 20 vol% comes in two separate forms:

19.7—Hb

0.3—dissolved in the plasma

1.2 Plasma Oxygen

- Represents an insignificant form delivered to the tissues.
- It is the dissolved and only the dissolved that creates the PO_2.
- There is a direct linear relationship between dissolved O_2 and PO_2.
- PO_2 can be considered a force that maintains that attachment of O_2 on Hb.
- High-affinity Hb site needs only a low PO_2 to maintain O_2 attachment.
- Lower-affinity Hb site needs a higher PO_2 to maintain O_2 attachment.



▲ **Figure 21–1.2** Oxygen Content of Blood vs. Plasma

1.3 Hemoglobin Oxygen

- An Hb molecule has four sites that bind oxygen.
- Each site has a different affinity for oxygen.
- When oxygen (or CO) binds to a site, all four sites gain affinity (cooperative binding).
- Oxyhemoglobin (0_2Hb or OxyHb) is the only significant form in which O_2 is delivered to the tissues.

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- Hb × 1.34 × S_aO_2/100 = blood O_2 content
- 15 g/100 mL × 1.34 × 97/100 = 19.5 vol% plus dissolved O_2 ≈ 20 vol%
- Carrying capacity = Maximum oxygen that can be carried in a given volume of blood attached to Hb

Hb site 4 • O_2 ← 100 mmHg — Hb 97% saturated, normal systemic arterial blood

Hb site 3 • O_2 ← 40 mmHg — Hb 75% saturated, normal systemic venous blood

Hb site 2 • O_2 ← 26 mmHg — Hb 50% saturation, P_{50} = PO_2 required for 50% sat

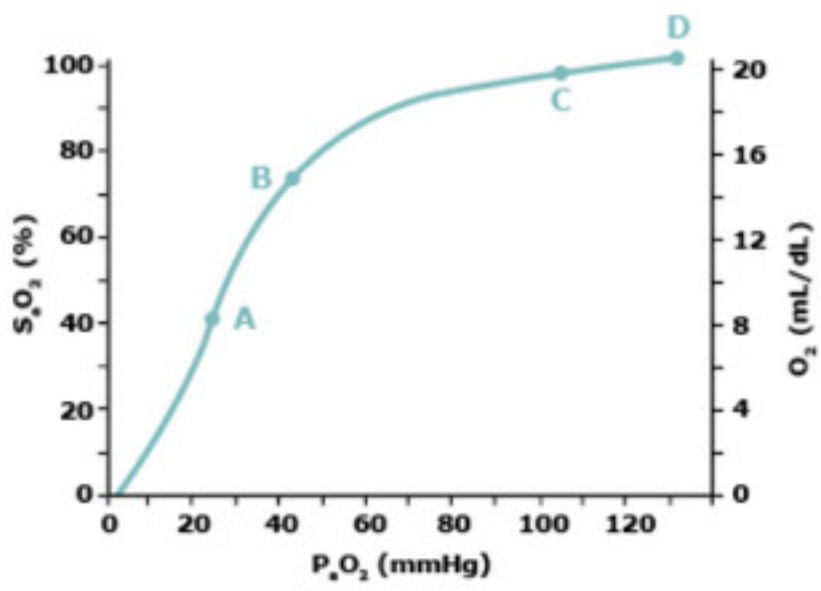
Hb site 1 • O_2 ← Under physiological conditions, this oxygen remains attached to Hb.

Blood entering systemic capillary PO_2 = 100 mmHg, Hb 97% saturated.

To unload the oxygen from site 4, the PO_2 of the plasma must drop below 100 mmHg, which means some dissolved O_2 must diffuse to the tissue. To unload the oxygen from site 3, the PO_2 must drop below 40 mmHg.

These are just approximate numbers. Depending on the chemical composition of the blood, changes occur in the binding site affinities; the P_{50} can change. If affinity decreases the P_{50}↑. A higher PO_2 is required to keep the O_2 on the second site.

1.4 Oxygen–Hemoglobin Dissociation Curves



▲ **Figure 21–1.4A** O_2-Hb Dissociation Curve

A = P_{50}, PO_2 = 26 mmHg
B = systemic venous blood, PO_2 = 40 mmHg, O_2 content 15 vol%
C = systemic arterial blood, PO_2 = 100 mmHg, O_2 content 20 vol%
D = systemic arterial blood with hyperventilation, PO_2 = 130 mmHg, O_2 content 20.1 vol%

Note: As the PO_2 decreases below 100 mmHg, there is initially a large decrease in PO_2 but only a slight decrease in O_2 content.

Important Concept

If CO (200 × the affinity for Hb vs. O_2) attaches to site 4 in the pulmonary capillary, O_2 on the remaining Hb sites is bound more strongly (cooperative binding). This causes a shift in the curve to the left, and the O_2 on those sites is essentially not available to tissues.

Giving 100% oxygen increases the force of O_2 (PO_2↑) and more quickly displaces the CO. In a hyperbaric chamber (PO_2↑↑↑) CO is displaced even quicker and at the extremely elevated plasma PO_2, it becomes a significant form delivered to the tissues.

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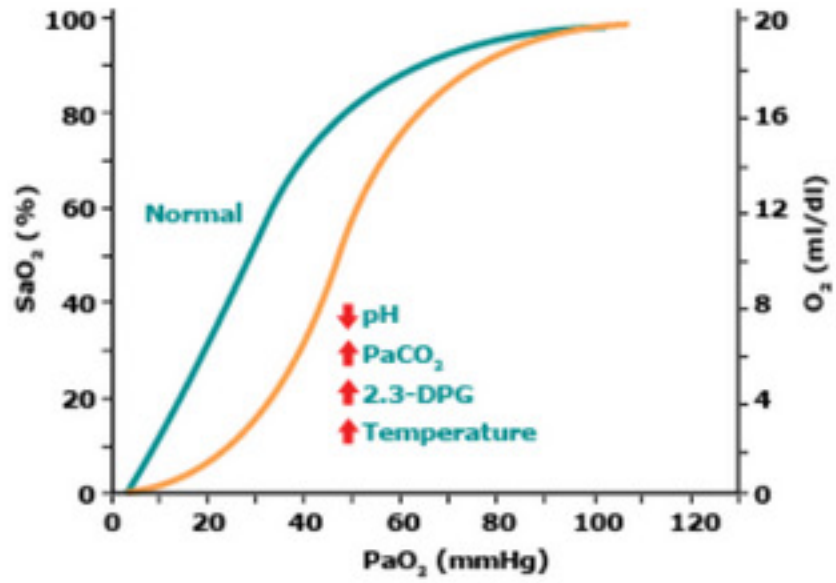
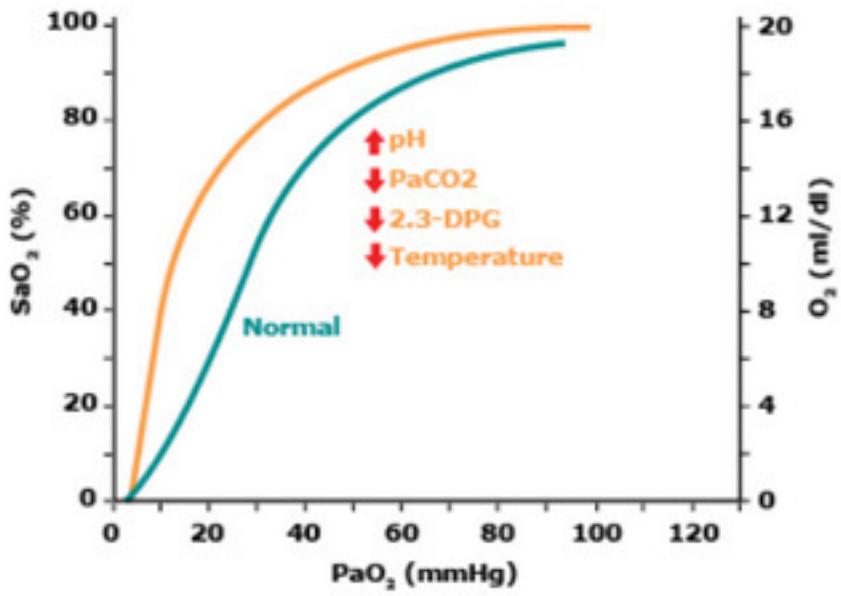
1.4.1. Shift to the Right



▲ **Figure 21–1.4B** O_2-Hb Dissociation Curve: Shift to the Right

- Decreased Hb affinity
- O_2 content ↓ at a given PO_2, steep part of the curve
- Favors unloading to the tissues over loading in the lung
- P_{50}↑
- Carrying capacity unchanged (plateau unchanged)

1.4.2. Shift to the Left



▲ **Figure 21–1.4C** O_2-Hb Dissociation Curve: Shift to the Left

- Increased Hb affinity
- O_2 content ↑ at a given PO_2, steep part of the curve
- A tendency toward loading in the lung over unloading to the tissues
- P_{50}↓
- Carrying capacity unchanged (plateau unchanged)
- Stored blood loses 2, 3-diphosphoglycerate
- Fetal hemoglobin shifted to the left

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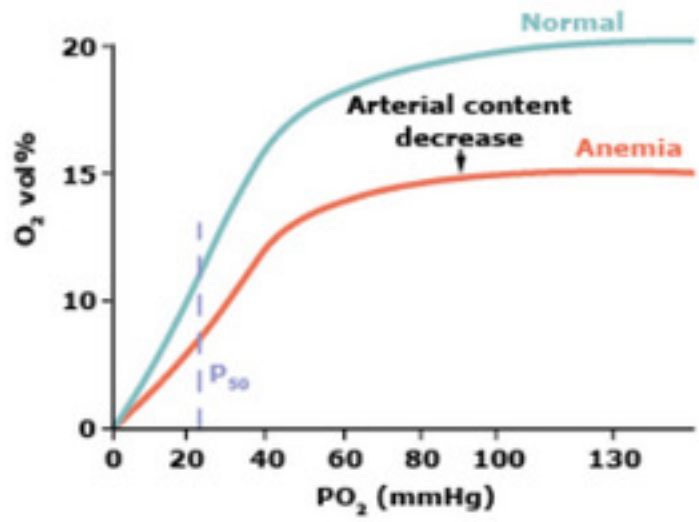
1.5 Pathophysiology

1.5.1 Anemia

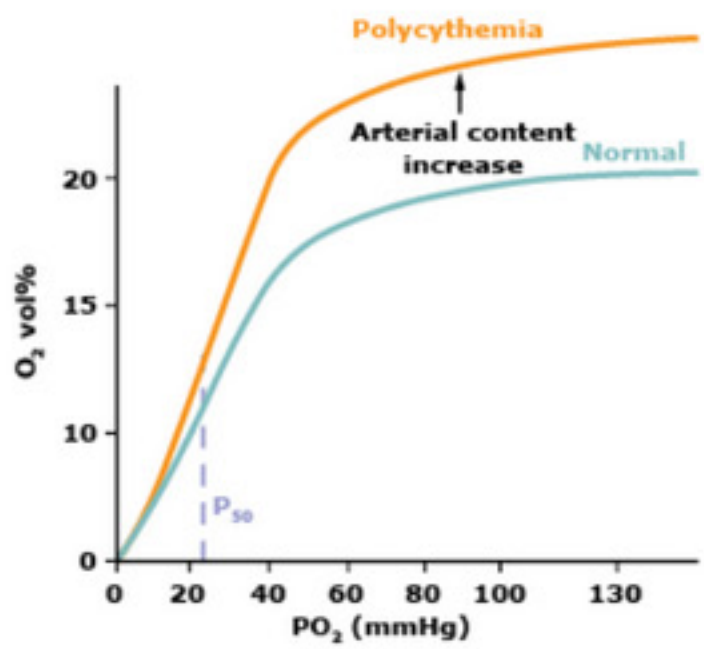


▲ **Figure 21–1.5A** O_2-Hb Dissociation Curve: Anemia

- Decreased Hb concentration
- Arterial PO_2 normal (100 mmHg)
- Saturation normal (O_2 per g Hb)
- O_2 content ↓
- Carrying capacity ↓ (less oxygen carried attached to Hb per mL of blood)

Note: Affinity normal, but with hypoxia and ↑ in 2,3-diphosphoglycerate, will shift the curve to the right.

1.5.2 Polycythemia



▲ **Figure 21–1.5B** O_2-Hb Dissociation Curve: Polycythemia

- Increased Hb concentration
- Arterial PO_2 normal
- Saturation normal (O_2 per g Hb)
- O_2 content ↑
- Carrying capacity ↑ (more oxygen carried attached to Hb per mL blood)

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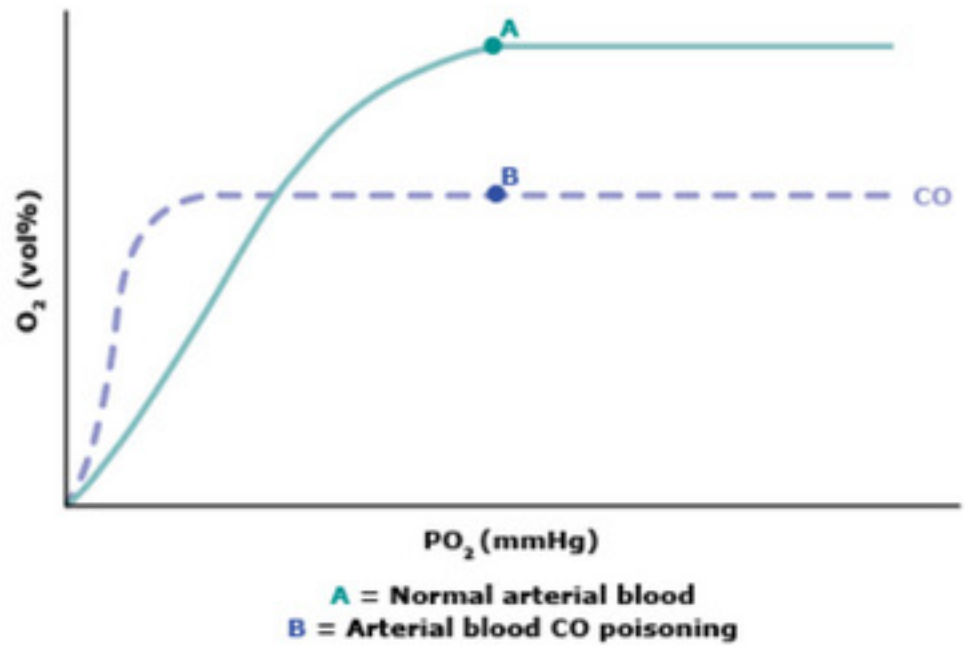
1.5.3 Carbon Monoxide Poisoning



▲ **Figure 21–1.5C** O_2-Hb Dissociation Curve: CO Poisoning

- Normal Hb concentration (acute poisoning)
- Arterial PO_2 normal (on room air)
- Saturation ↓
- O_2 content ↓
- Carrying capacity ↓ (less O_2 carried attached to Hb per mL blood)

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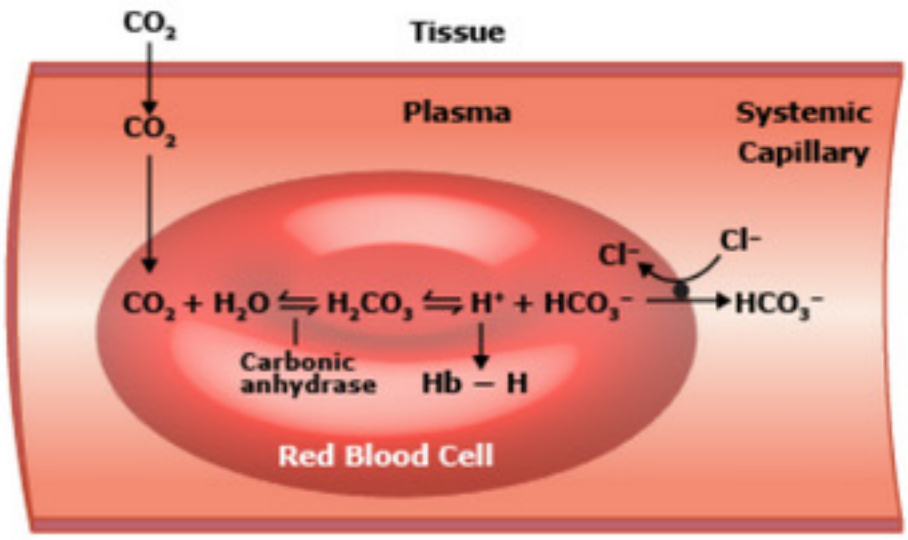
2 Carbon Dioxide Transport

Because CO_2 is so soluble in water, a significant amount is carried dissolved in the plasma (5%). An equivalent amount is carried as carbamino (CO_2 attached to protein, mainly Hb) compounds, but most of the CO_2 is carried as plasma HCO_3.



▲ **Figure 21–2.0** Conversion of CO_2 Into Bicarbonate in an RBC

- No plasma carbonic anhydrase.
- CO_2 diffuses from tissue to red blood cell.
- In RBC the CO_2 is converted to H^+ and HCO_3^- catalyzed by carbonic anhydrase.
- HbO_2 to Hb greatly increases its buffer capacity.
- H^+ buffering by Hb shifts the reaction toward HCO_3^-.
- HCO_3^- transported to the plasma in exchange for Cl^-.

Important Concept

HCO_3^- is formed in the red blood cell but carried in the plasma.

The main form of CO_2 in the blood is plasma HCO_3^-.

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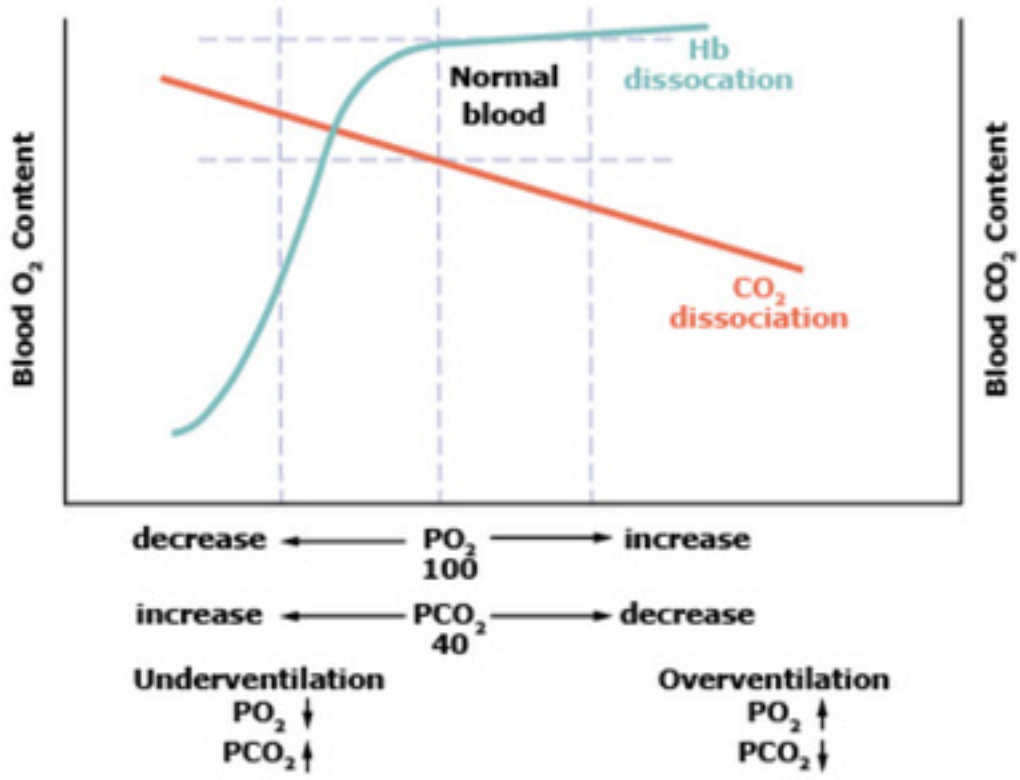
3 Hemoglobin Dissociation Curve vs. CO_2 Dissociation Curve



▲ **Figure 21–3.0** O_2 vs. CO_2 Blood Content Changes With Under- and Over-Ventilation

3.1 Summary

- An overventilated lung region (blood leaving ↑ PO_2) *does not* compensate for an underventilated lung region (blood leaving ↓ PO_2) in terms of oxygen content of the blood. The individual will have hypoxemia (↓ arterial oxygen content ↓ arterial PO_2).
- An overventilated lung region (blood leaving ↓ PCO_2) *does* compensate for an underventilated lung region (blood leaving ↑ PCO_2) in terms of CO_2 content and PCO_2. The individual will not necessarily have hypercapnia and may have hypocapnia.

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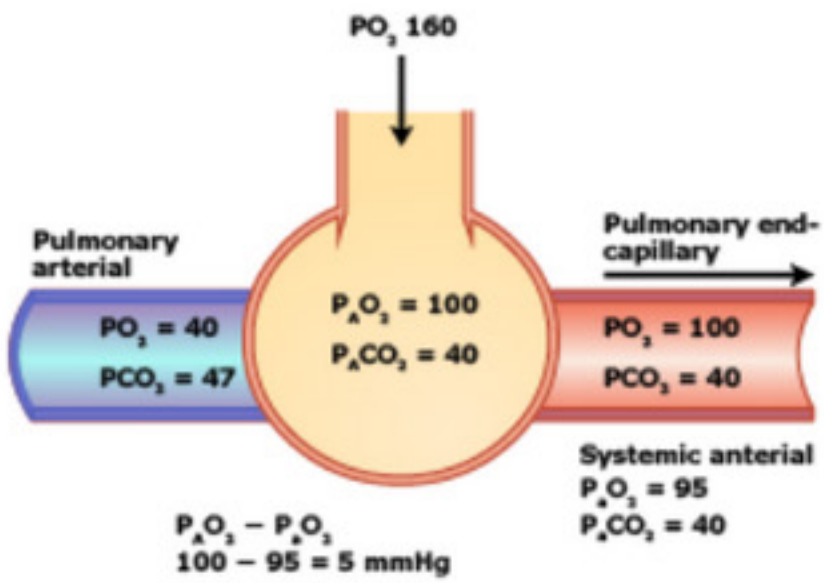
1 High Altitude

1.1 Normal Individual at Sea Level

In a normal individual at sea level, the alveolar compartment, pulmonary end-capillary, and systemic arterial blood have approximately the same PO_2 and PCO_2. End-tidal air reflects the alveolar compartment. The natural shunting of blood through the lungs causes a slight drop in systemic arterial PO_2. This is expressed as an A–a PO_2 gradient. It is normal for the gradient to be 5–8 mmHg. A value above 10 denotes pulmonary disease.

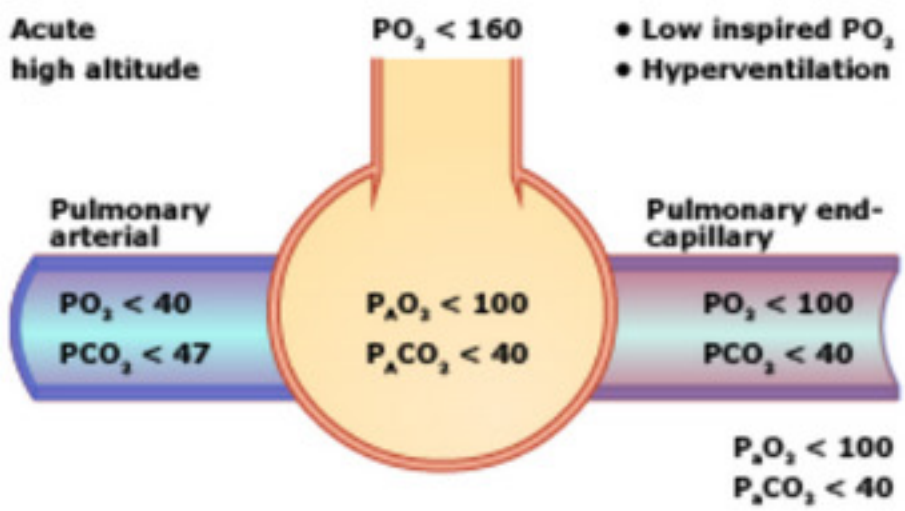


▲ **Figure 22–1.1** PO_2 and PCO_2 in Pulmonary Compartments: Normal Person at Sea Level

1.2 Acute Changes at High Altitude

At high altitude, low-pressure oxygen is inspired. Consequently, $P_AO_2 < 100$ mmHg, $P_aO_2 < 100$ mmHg. The low P_aO_2 stimulates the peripheral chemoreceptors, initiating a hyperventilation and a $P_ACO_2 < 40$ mmHg and a $P_aCO_2 < 40$ mmHg.

Thus, acutely at high altitude the *main* drive for ventilation is the low PO_2 on the peripheral receptors. The hyperventilation and low PCO_2 reduces the central drive for ventilation.



▲ **Figure 22–1.2** PO_2 and PCO_2 in Pulmonary Compartments: High Altitude

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Acute respiratory alkalosis—Arterial pH > 7.400, P_ACO_2 < 40 mmHg, HCO_3^- slightly depressed but usually still in the normal range.

1.3 Adaptation to High Altitude

PO_2: P_AO_2 and P_aO_2 are permanently depressed unless supplemental O_2 administrated.

PCO_2: The increased CSF pH returned toward normal, a greater stimulus to the central receptors and, if anything, a further increase in alveolar ventilation.

pH: The kidney compensates for the alkalosis. In this case there is a complete or almost complete compensation. Arterial pH returns to the normal range after a few days. HCO_3 loss and an alkaline urine are formed only during compensation. Once compensation is complete, urine pH returns to its normal value, which is usually in the acidic range.

Hb: Within the first day, hypoxia elevates the circulating levels of erythropoietin, which increases the production of RBCs and their rate of maturation, making polycythemia evident about three weeks later.

Hb sat: Since the inspired PO_2 remains depressed, Hb saturation remains depressed unless supplemental O_2 is administered.

Arterial O2 content: Acutely depressed due to decreased saturation of a normal Hb concentration. Oxygen content returns toward normal not because of a change in Hb saturation, but because of an increase in the Hb concentration.

Summary of systemic arterial blood after adaptation:

P_aO_2 ↓
P_aCO_2 ↓
pH normal (within 1 week)
Hb sat ↓
Hb ↑ (within 1 month)
O_2 content normal (within 1 month)

1.4 Hyperbaric Environment

PO_2 and PN_2 increases in the alveoli and the systemic arterial blood. Increased PO_2 can cause oxygen toxicity, and increased PN_2 can cause nitrogen narcosis. In addition, a scuba diver who suddenly decompresses can suffer *the bends*, or Caisson disease. Nitrogen bubbles can form in the tissues and blood. Treatment is a recompression and a slow decompression, or breathing 100% oxygen. This replaces the nitrogen in the inspired air and accelerates the nitrogen washout.

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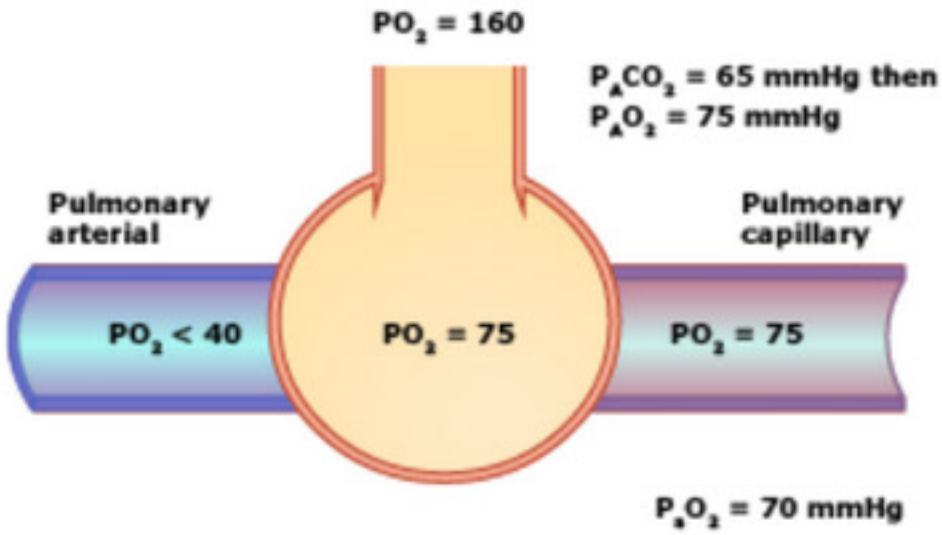
2 Hypoventilation

Elevates the P_ACO_2. The increase in P_ACO_2 decreases the P_AO_2. Assuming R = 1.0, an increase in P_ACO_2 produces an equivalent decrease in P_AO_2. If P_ACO_2 increases from 40 to 65 mmHg, P_AO_2 decreases from 100 to 75 mmHg. Assuming no additional problems in the respiratory system exist, P_aO_2 would also decrease by 25 mmHg. So, with hypoventilation, there will be equal changes in the alveolar and systemic arterial systems, and thus no widening of the A–a gradient.

Since P_aO_2 is depressed, systemic venous and pulmonary arterial PO_2 are also depressed.



▲ **Figure 22–2.0** PO_2 and PCO_2 in Pulmonary Compartments: Hypoventilation

2.1 Summary

- Returning ventilation to normal returns PCO_2 and PO_2 to normal.
- Supplemental O_2 returns P_AO_2 and P_aO_2 to normal.
- As long as the decrease in alveolar ventilation is fairly uniform throughout the lung, no widening of the A–a gradient (P_AO_2 from end-tidal air).
- Gas exchange is not a problem and oxygen delivery is still perfusion limited.

Important Concept

High altitude and hypoventilation are the two causes of hypoxemia that originate from a low alveolar PO_2.

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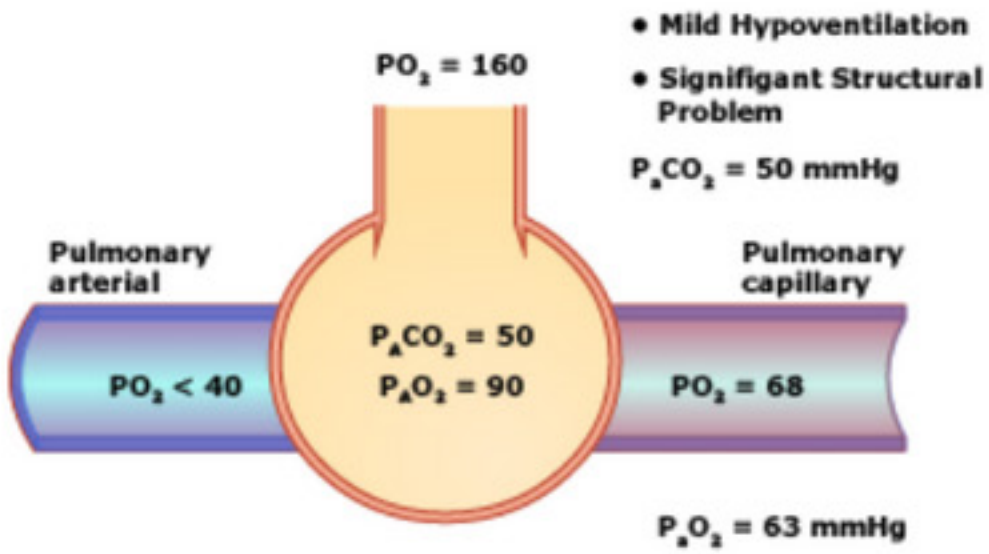
3 Diffusion Impairment

Diffusion impairment is equivalent to a structural problem in the lung tissue that affects gas exchange. It can be a loss of surface area, as occurs in emphysema, and/or an increase in the thickness of the membranes, as occurs in fibrosis. A significant structural problem is a diffusion-limited situation.

In many cases, a structural problem produces mechanical problems, and there are degrees of hypoventilation.



▲ **Figure 22–3.0** PO_2 and PCO_2 in Pulmonary Compartments: Diffusion Impairment

3.1 Summary

- Pulmonary end-capillary $PO_2 < P_AO_2$
- Diffusion-limited situation
- Widening of the A–a gradient
- End-tidal air does not reflect systemic arterial levels
- Supplemental O_2 returns P_aO_2 toward normal
- Decrease in DL_{CO}

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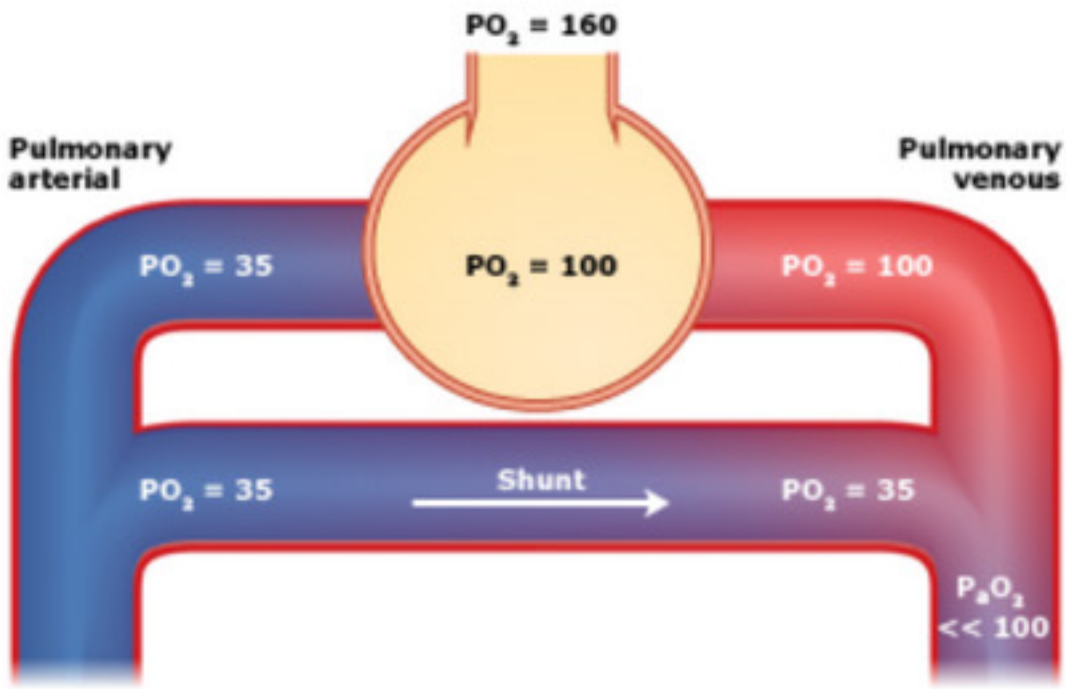
4 Pulmonary Shunt

A pulmonary shunt is blood passing through the pulmonary circulation and entering the left heart without changing its chemical composition. In the shunted region, pulmonary arterial PO_2 equals pulmonary venous PO_2. A pulmonary shunt is also referred to as a *right-to-left shunt*. A regional atelectasis created by a pneumothorax is an example of a pulmonary shunt.



▲ **Figure 22–4.0** PO_2 in Pulmonary Compartments: Pulmonary Shunt

- P_aO_2 is below pulmonary end-capillary and P_AO_2 in the well-ventilated lung regions. If pulmonary end-capillary PO_2 is listed as normal with hypoxemia, pulmonary shunt is the most likely possibility.
- Widening of the A–a gradient and thus end-tidal air does not reflect P_aO_2.
- The most significant characteristic of a pulmonary shunt is that giving supplemental O_2 raises P_AO_2, but there is no significant increase in P_aO_2. Hyperventilation, as might occur with a pneumothorax (normal lung regions) also does not relieve the hypoxemia but may induce hypocapnia.

4.1 Summary

- P_aO_2 < pulmonary end-capillary and P_AO_2
- Widening of the A–a gradient
- Supplemental O_2 not effective at elevating P_aO_2
- Hyperventilation does not elevate P_aO_2 but may cause hypocapnia.

Important Concept

Most important point: Failure of supplemental O_2 to obtain a significant rise in P_aO_2 is diagnostic for a pulmonary shunt. A significant rise in P_aO_2 with supplemental eliminates shunt as a possibility.

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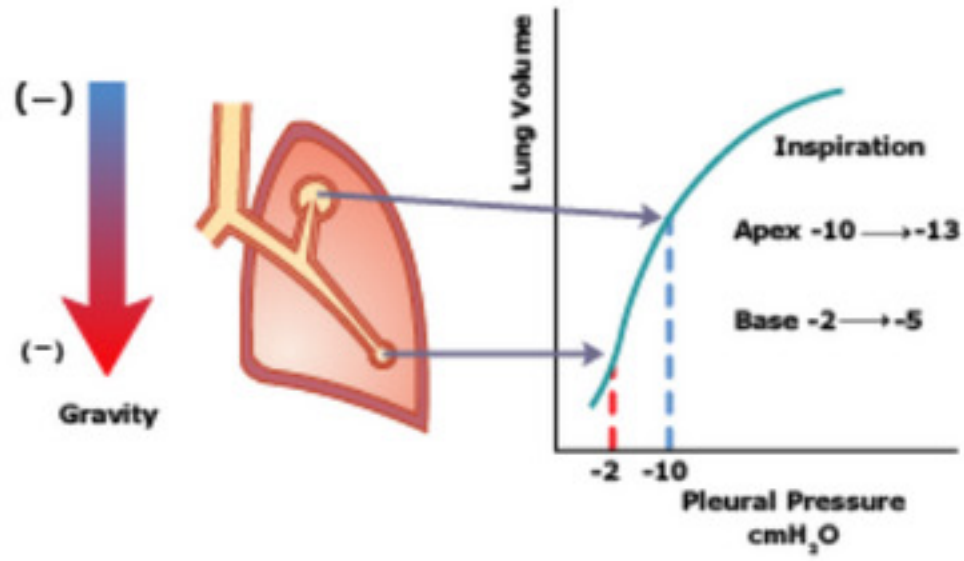
5 Ventilation-Perfusion Differences

Because of the effect of gravity, pleural pressures and pulmonary blood pressure will increase from the apex toward the base of the lung. This causes regional differences in ventilation and blood flow.



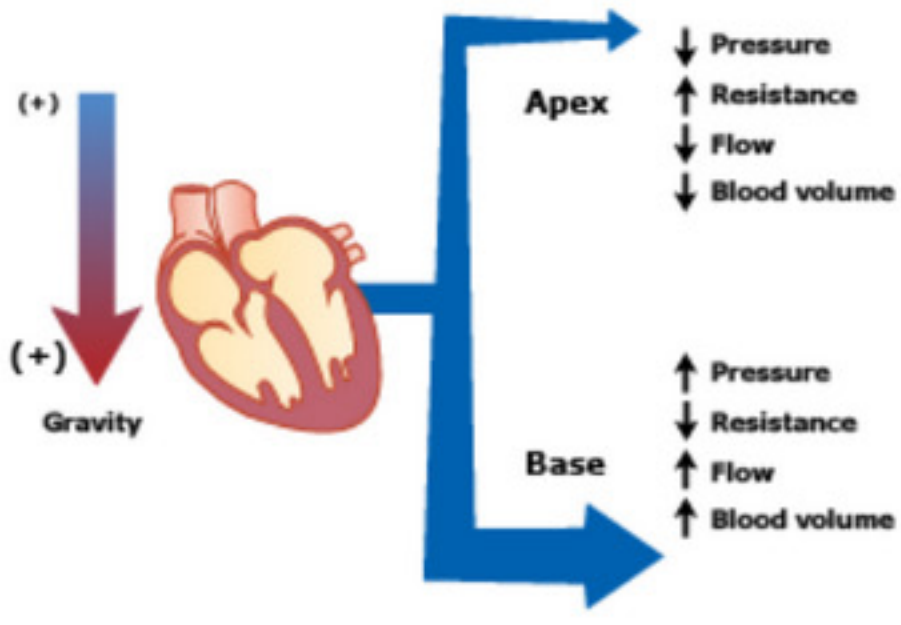
▲ **Figure 22–5.0** Base-Apex Differences in Ventilation Due to Gravity

5.1 Ventilation

- **Apex:** At FRC, pleural pressure is about −10 cmH_2O. This expanding force results in larger, less-compliant, stiffer alveoli at the apex. The less-compliant nature of these alveoli means that less air flows into the apical alveoli during inspiration.
- **Base:** At FRC, pleural pressure is about −2 cmH_2O. This smaller expanding force results in smaller, more compliant alveoli at the base. The greater compliance at the base means more air flows into the base alveoli during inspiration. They are smaller than the apical alveoli during the entire respiratory cycle, but have a greater change in size, and overall alveolar ventilation is greater at the base than at the apex.

5.2 Blood Flow

- **Apex:** When blood flows up toward the apex, pressure decreases. The vessels become less distended (pulmonary vessels are very compliant) and have a greater resistance. Thus, apex receives the least blood flow and the vessels contain a small volume of blood.
- **Base:** When blood flows down toward the base, pressure increases, the vessels are more distended and have a lower resistance. Thus, the base receives the greatest blood flow and the vessels contain a large blood volume.



▲ **Figure 22–5.2** Base-Apex Differences in Blood Flow Due to Gravity

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Arterial and venous pressures increase toward the base, and other factors, such as alveolar pressure, also affect the distribution of flow. But overall, good perfusion pressure and a low-resistance pathway mean that the base receives the greatest blood flow.

5.3 $\dot{V}_A/Q$

Blood entering the pulmonary circulation under resting conditions has a PO_2 of about 40 mmHg. Oxygen is added to the pulmonary capillary blood via alveolar ventilation until ideally the Hb is saturated with oxygen (PO_2 100 mmHg).

At rest, pulmonary blood flow (Q) is 5L/min (CO). The alveolar ventilation ($\dot{V}_A$) necessary to supply the oxygen to saturate the Hb as the blood passes through the capillaries is about 4L/min. Thus:

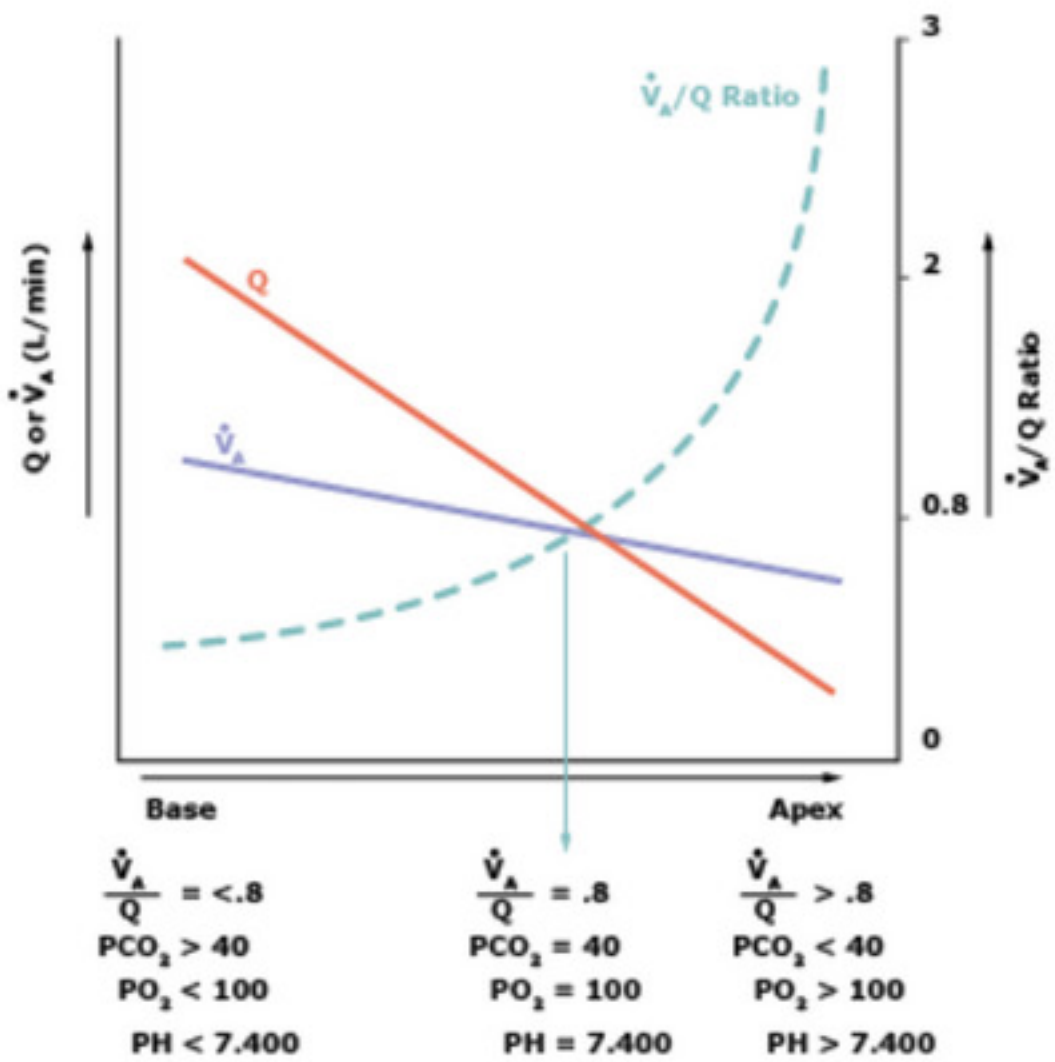
$$\dot{V}_A/Q = 4000 \text{ mL}/5000\text{mL} = 0.8$$

This represents our ideal lung unit at rest:

PCO_2 = 40 mmHg

PO_2 = 100 mmHg

pH = 7.400 (blood leaving the capillary)



▲ **Figure 22–5.3** Base-Apex Differences in $\dot{V}_A/Q$ Due to Gravity

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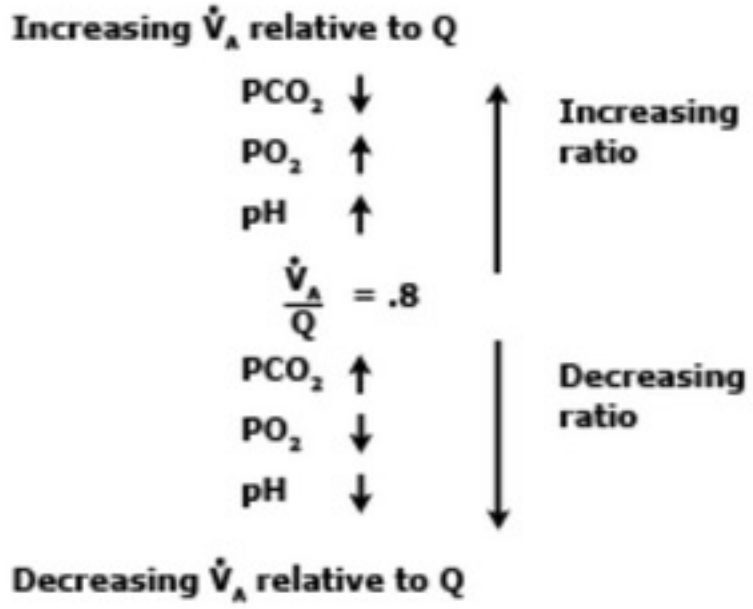
5.4 Evaluation $\dot{V}_A/Q$



▲ **Figure 22–5.4** Effect of Ventilation on V•A/Q, PCO_2, PO_2, pH

Evaluate these resting lung units for deviations from the ideal PCO_2, PO_2, and pH of the blood leaving the capillary.

$\dot{V}_A/Q$

1. 0.71
2. 0.65
3. 1.03

In addition, if there is a significant decrease in the P_AO_2 below 100 mmHg (not blood PO_2), there is a vasoconstriction in the perialveolar vessels. This is referred to as *hypoxic vasoconstriction*. It is a phenomenon unique to pulmonary circulation.

Evaluate and compare to the ideal lung unit.

$$\dot{V}_A/Q = 0.7$$

Does this lung unit exhibit hypoxic vasoconstriction?

What are the consequences of a greater degree of hypoxic constriction?

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5.5 Generalizations of $\dot{V}_a/Q$ Mismatches

5.5.1 $\dot{V}_A/Q < 0.8$

- Lung unit underventilated: $PCO_2 > 40$ mmHg, $PO_2 < 100$ mmHg.
- As the ratio decreases, it approaches zero.
- If ratio = zero: blood flow, but no ventilation (pulmonary shunt).
- As the ratio decreases below 0.8, it has a shunt component.
- Low ratios cause hypoxemia.

5.5.2 $\dot{V}_A/Q > 0.8$

- Lung unit overventilated: $PCO_2 < 40$ mmHg, $PO_2 > 100$ mmHg.
- As the ratio increases, it approaches infinity.
- If ratio = ∞: ventilation, but no blood flow (alveolar dead space).
- As the ratio increases above 0.8, it has a dead space component.
- High ratios do not cause hypoxemia.

In patients with $\dot{V}_A/Q$ mismatch, some lung units have high ratios whereas others have low ratios. High ratios do not cancel the low ratios in terms of PO_2, and the patients will have hypoxemia. However, high ratios can cancel low ratios in term of PCO_2, and the patients may not have hypercapnia. Instead, it is possible to see the hypoxemia associated with a hypocapnia.

The nonuniform ventilation and blood flow causes a widening of the A–a gradient. Supplemental oxygen usually causes a significant rise in P_aO_2, but as the ratios decrease, the shunt component increases, and the patient is less responsive to supplemental oxygen.

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Unit 7

Renal Physiology

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1 Basic Concepts

1.1 Homeostasis

The kidney plays a crucial role in the regulation of the following:

- Total body fluid volume and intravascular volume.
- Body fluid osmolarity.
- Serum electrolytes (Na^+, K^+, Ca^{++}, etc.).
- Acid-base balance.

1.2 Renal Processes

- **Filtration:** Fluid and electrolytes enter the nephron system at the level of the glomerulus (passive).
- **Reabsorption:** Water and dissolved substances that were originally filtered are returned back into the bloodstream (active and passive).
- **Secretion:** Substances enter the nephron system at any point beyond the glomerulus (mainly active).
- **Excretion:** Fluid and dissolved substances that are lost in the urine.

1.3 Endocrine Function

- The kidney secretes erythropoietin, which stimulates red blood cell production in the bone marrow.
- The kidney secretes renin, which regulates blood volume, blood pressure, and electrolyte balance.
- The kidney activates vitamin D, converting 25-hydroxy vitamin D to 1, 25-dihydroxy vitamin D (calcitriol).

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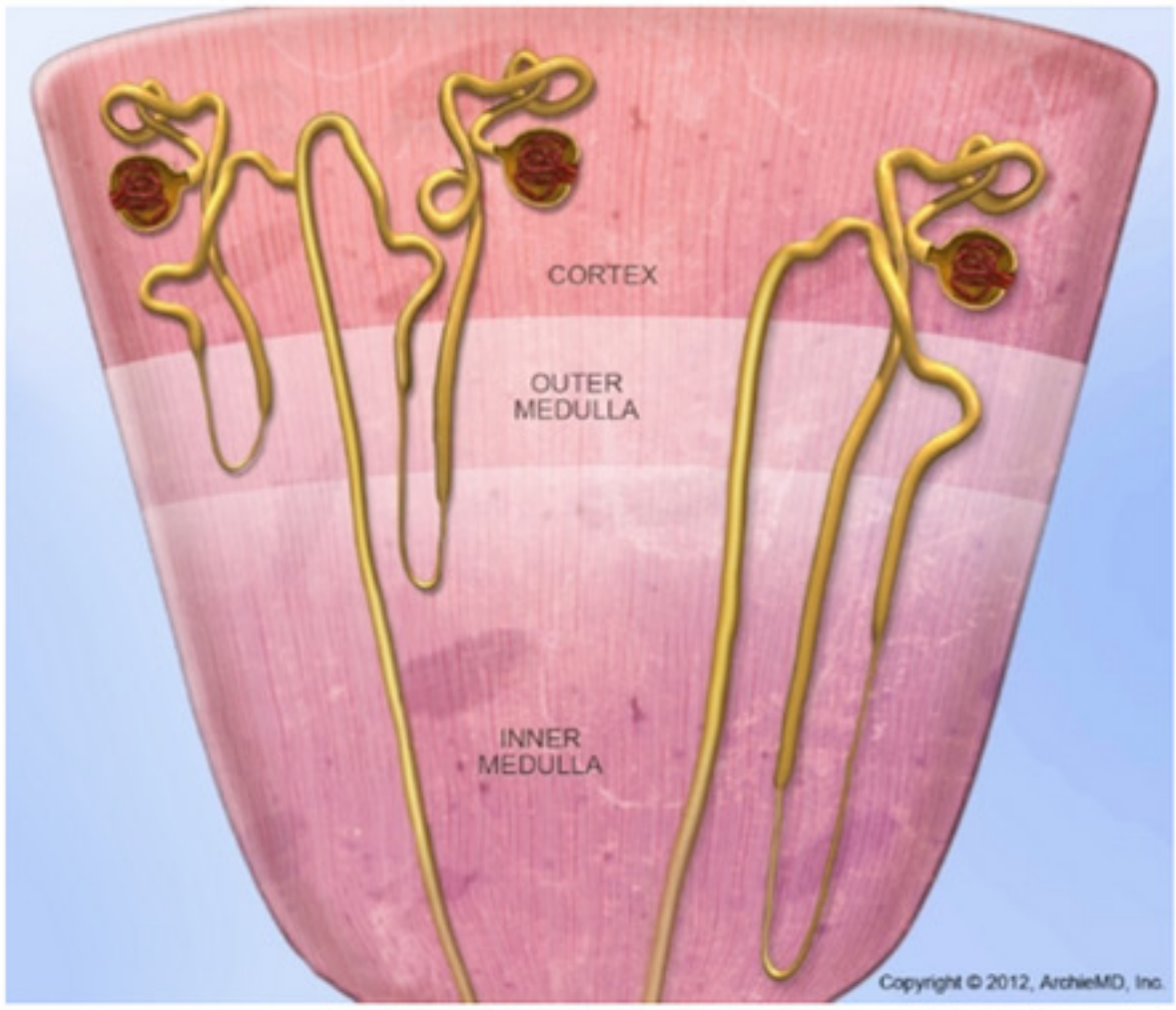
2 Renal Structural and Functional Anatomy

2.1 Renal Functional Anatomy



▲ **Figure 23–2.1** Organization Within the Kidney

Cortical Nephrons: Glomeruli in the outer cortex. Short loops of Henle that only reach the outer medulla (85–90% of all nephrons).

Juxtamedullary Nephrons: Glomeruli in the inner cortex. Long loops of Henle, which extend into the inner medulla (10–15% of all nephrons).

2.2 Nephron Structure and Blood Supply

Nephrons are composed of:

- Glomerulus
- Proximal convoluted tubule
- Loop of Henle
- Distal convoluted tubule
- Cortical collecting duct
- Medullary collecting duct

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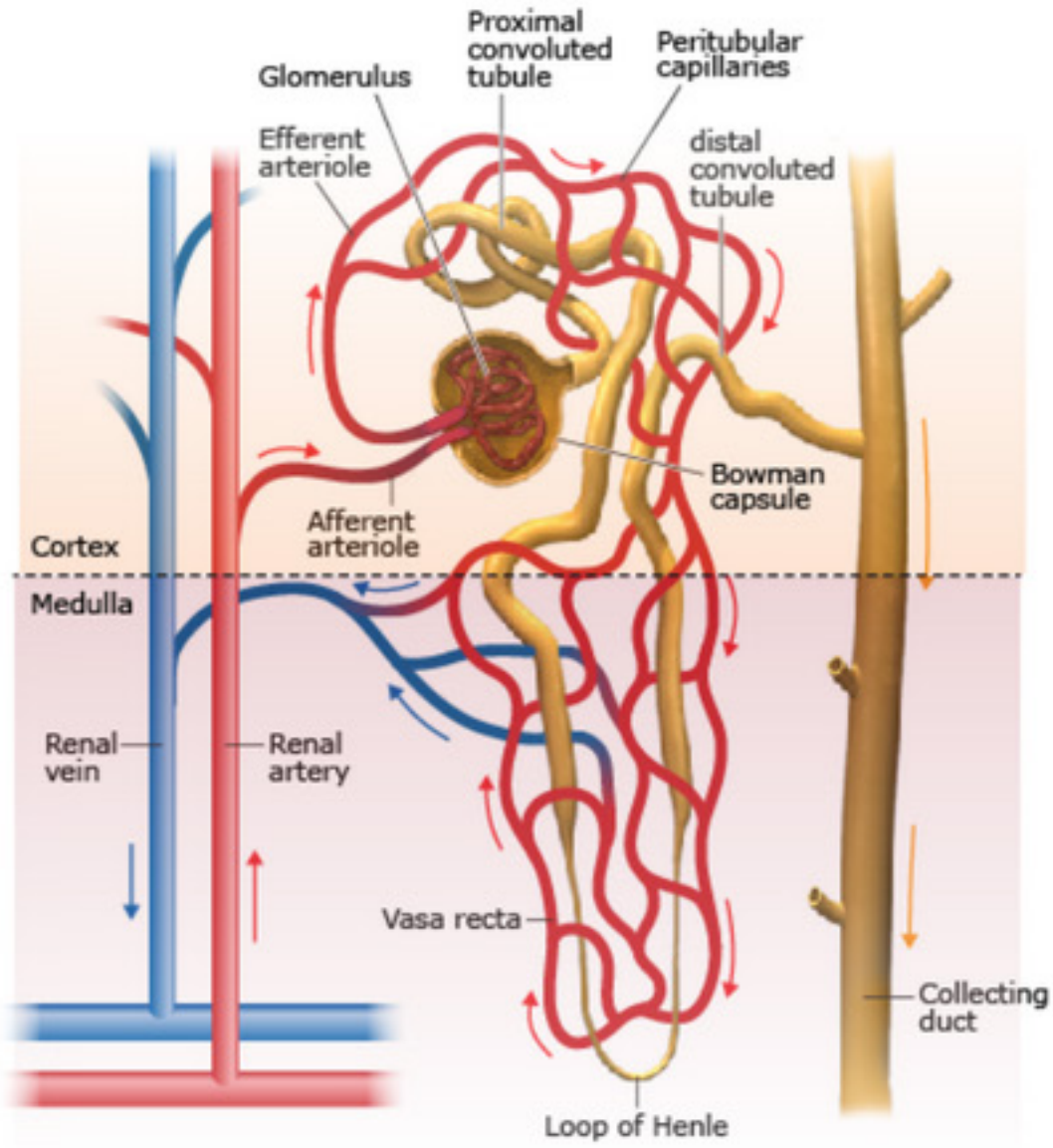

▲ **Figure 23–2.2** Nephron Vasculature

2.2.1 Blood Supply (Series System)

Afferent Arteriole: High-resistance vessel, delivers blood to glomerular capillaries.

Glomerular Capilliaries: High pressure filtering capillaries.

Efferent Arteriole: High-resistance vessel, delivers blood to peritubular apillaries and vasa recta.

Peritubular Capillaries: Low pressure reabsorbing surrounding the renal tubules in the cortex.

Cortex Interstitium: An isotonic environment (300 mOsm).

Vasa Recta: Low-flow capillary loops providing a countercurrent system in the medullary interstitium. Allows the reabsorption of water and electrolytes, without disrupting interstitial osmolar gradient (300 outer medulla and up to 1200 mOsm inner medulla).

2.3 Renal Blood Flow

The kidney receives 20–25% of the cardiac output and under normal conditions exhibits strong autoregulation. Flow is regulated mainly via the resistance of the afferent arteriole. Two mechanisms contribute:

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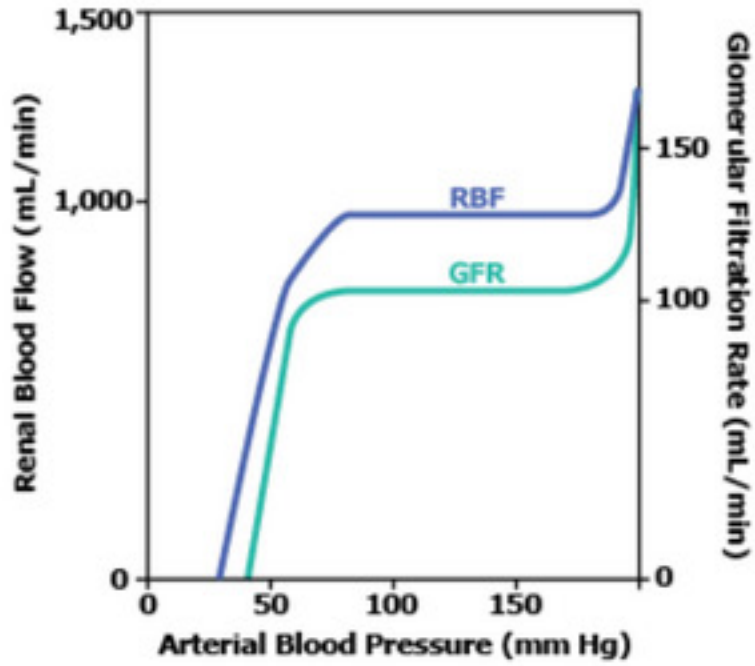
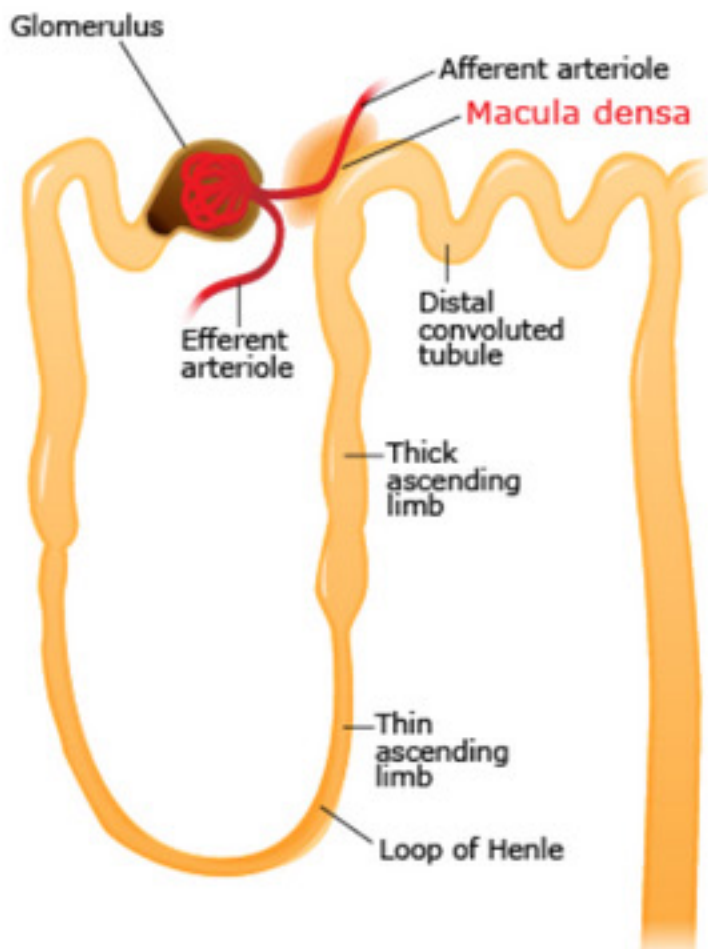


▲ **Figure 23–2.3A** Autoregulation of Renal Blood Flow and GFR

Myogenic Mechanism: Based on the intrinsic property of smooth muscle to contract when stretched.

Tubuloglomerular Feedback: The macula densa, sensory cells located at the top of the ascending limb of the loop of Henle, monitor the delivery of NaCl (or possibly just Cl) as an index of GFR. Decreased NaCl dilates the afferent arteriole. Increased NaCl constricts the afferent arteriole (mediator possibly adenosine).



▲ **Figure 23–2.3B** Macula Densa in Relation to Afferent Arteriole

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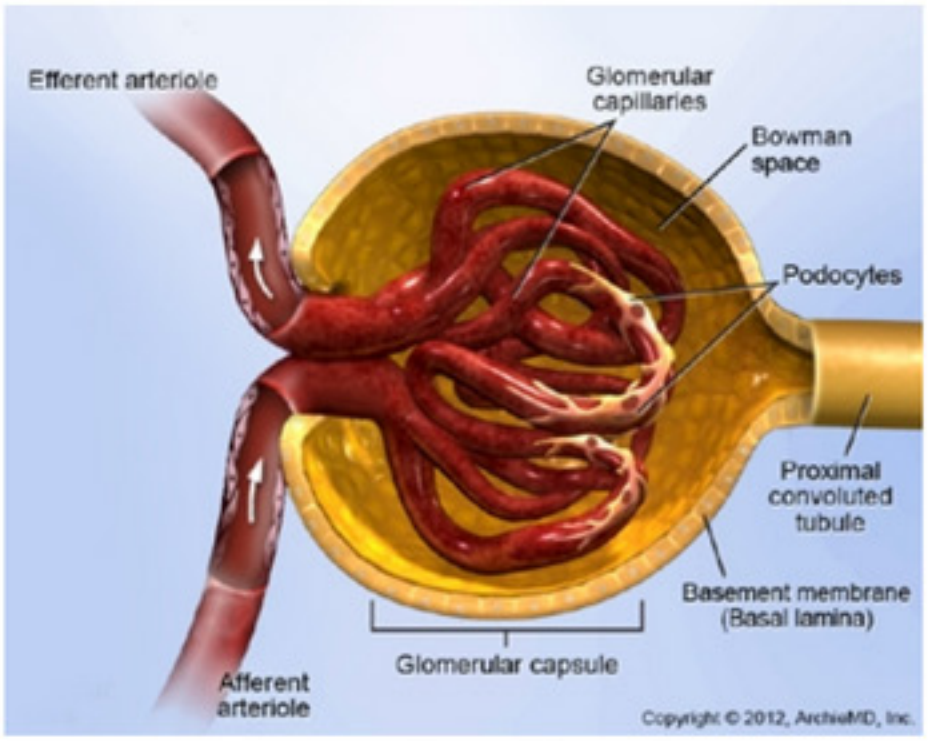
1 The Glomerulus



▲ **Figure 24–1.0** Glomerulus

- Filtration occurs in the glomerulus.
- Afferent arterioles enter the glomerulus and expand into a tuft of capillaries.
- These tufts increase the surface area of the capillaries dramatically, which greatly enhances the amount of filtration possible.

1.1 GFR

GFR is a volume of fluid filtered into Bowman space per unit time (volume/time). A typical value for a healthy young individual is 120 mL/min or 180 L/day. If an individual donates a kidney, GFR is not reduced by 50%. The remaining kidney compensates and hypertrophies such that GFR is only reduced approximately 20–25%.

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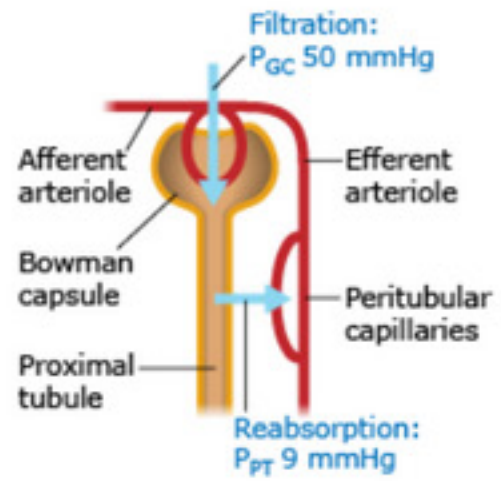
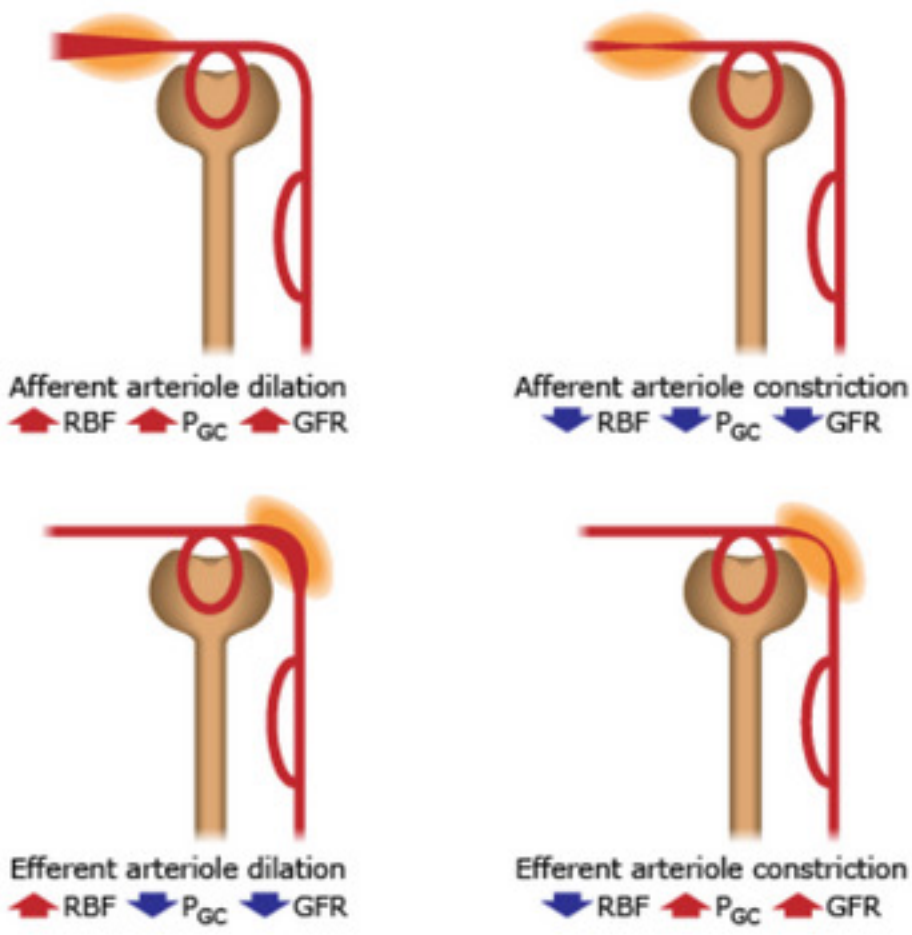
2 Glomerular Capillary Hemodynamics



P_{GC} = Pressure glomerular capillaries
P_{PT} = Pressure peritubular capillaries



RBF = Renal blood flow
P_{GC} = Pressure glomerular capillaries
GFR = Glomerular filtration rate

▲ **Figure 24–2.0** Effects of Resistance Changes in Afferent and Efferent Arterioles

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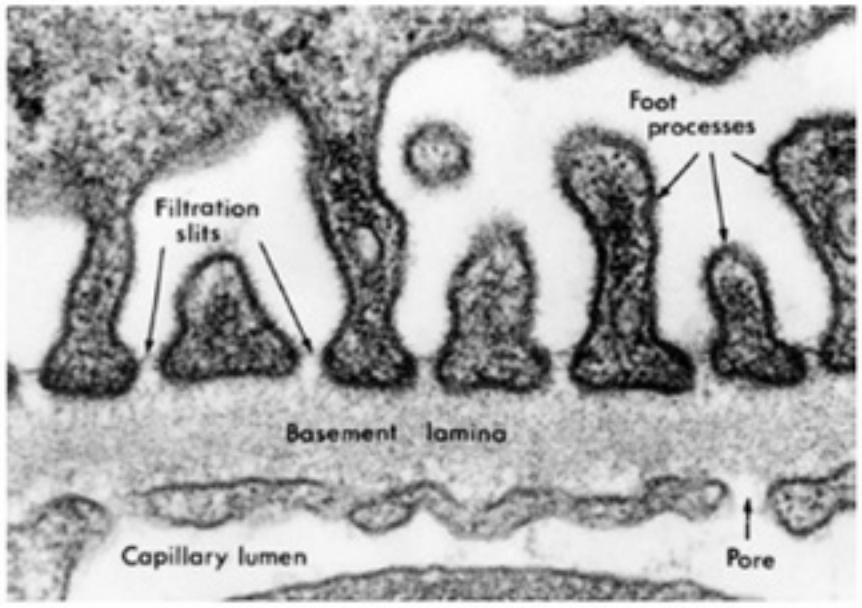
3 Filtration Barrier

3.1 Layers of Filtration Barrier

There are three layers of renal filtration barriers:

- **Blood side:** Fenestrated endothelial cells of glomerular capillaries (pore).
- **Glomerular basement membrane (lamina):** Negatively charged, which repels negatively charged proteins.
- **Urine side:** Podocytes (a.k.a. visceral epithelial cells), which lie over the glomerular basement membrane. Between podocytes are tyny openings, filtrations slits, which are covered by slit diaphragms.



Dr. Donald Fawcett & D. Friend/Visuals Unlimited, Inc.

▲ **Figure 24–3.1** Layers of Renal Filtration Barriers

3.2 Materials Freely Filtered by the Kidney

- Electrolytes: Na, K, Cl, HCO_3, Ca.
- Metabolites: glucose, amino acids, lactate, ketone bodies.
- Small proteins and peptides: growth hormone, insulin, glucagon, FSH, LH, hCG.
- Non-natural substances: mannitol, inulin, para-aminohippuric acid (PAH).

3.3 Materials Not Freely Filtered by the Kidney

- Large proteins, such as albumins and globulins.
- Lipid soluble substances bound to plasma proteins, such as T4, cortisol, progesterone, and estrogen; however, the free fraction of the lipid is filtered and appears in the urine (e.g., free cortisol).

3.4 Bowman Space Fluid

- If a substance is freely filtered, its concentration in the Bowman space is the same as in the plasma. The tubular fluid concentration divided by the plasma concentration is 1 (TF/P = 1.0).
- The osmolarity of the filtrate will be the same as the ECF (300 mOsm), mainly determined by two times the Na concentration.

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4 Pathophysiology

4.1 Minimal Change

- Minimal change: A type of primary glomerular disease in which the glomeruli appear normal on light microscopy.
- For unclear reasons, negative charges on the glomerular filtration barrier are lost.
- Proteins (particularly albumin) are able to pass through the basement membrane, resulting in proteinuria.

4.1.1 Etiology

- Vast majority are idiopathic.
- In adults, some cases are drug-induced (e.g., NSAIDs) or paraneoplastic (most commonly, Hodgkin lymphoma).

4.1.2 Clinical Prototype of Nephrotic Syndrome

- Most common cause of nephrotic syndrome in children.
- Accounts for ~ 10% of nephrotic syndrome in adults.

4.1.3 Diagnosis

- Often clinical in children.
  - Biopsy generally not needed as MCD accounts for vast majority of nephrotic syndrome in children.
- In adults, a biopsy is often required due to broader differential diagnosis.
- Disease is named for biopsy findings:
  - Normal light microscopy
  - *Effacement* (i.e., fusion) of foot processes on electron microscopy

4.1.4 Treatment: *Corticosteroids*

- Usually results in dramatic improvement.
- Failure to respond suggests alternative diagnosis (e.g., focal segmental glomerularsclerosis or FSGS).

4.2 Nephrotic Syndrome

- Noninflammatory injury to the glomerular membrane system.
- Damage is usually to the epithelial podocytes or the basement membrane.
- Proteinurea (>3.5 g/day).
- Some decrease in GFR but creatinine close to normal.
- Increased lipids and cholesterol in the blood.
- Loose gamma globulins, increased risk of infections.
- Hypercoagulability due to loss of anticoagulants in the urine.
- Hypoalbuminemia, decreased oncotic pressure, and peripheral edema.

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4.3 Nephritic Syndrome

- Inflammatory injury to the endothelium or the basement membrane.
- Significant decrease in GFR due to decreased surface area for filtration.
- Limited proteinurea.
- Oliguria and azotemia.
- Salt retention with periorbital (around the eyes) edema and hypertension.
- RBC casts in the urine.

A nephritic pattern is present in *Alport syndrome*, a glomerulonephritis caused by a defect in collagen that results in a thinning and splitting of the glomerular basement membrane.

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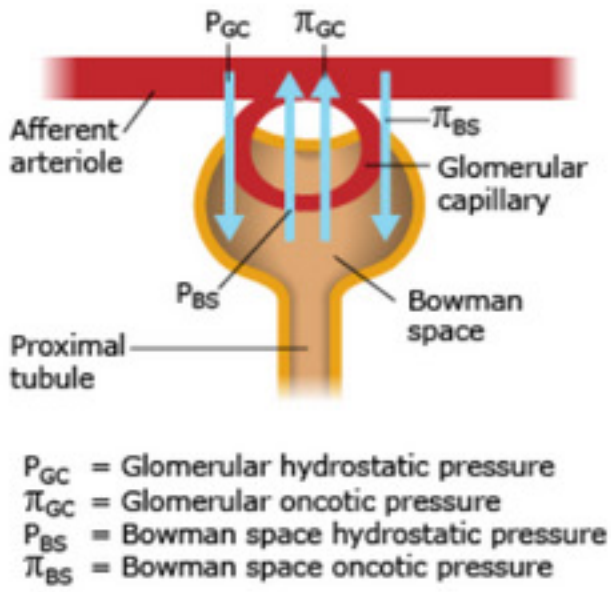
5 Determinants of Glomerular Filtration Rate



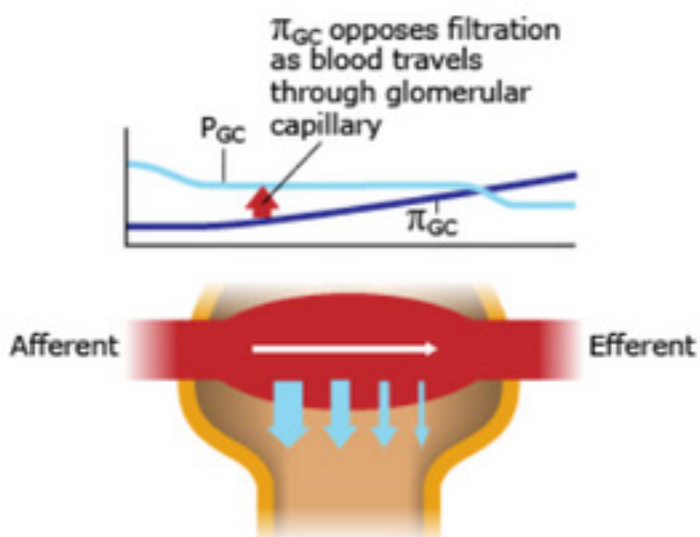
▲ **Figure 24–5.0** Factors Determining Glomerular Filtration Rate

5.1 Hydrostatic Pressure in Glomerular Capillaries (P_{GC})

This is the main force promoting and determining GFR. It is controlled and maintained within the normal range via changes in resistance of the afferent arteriole (autoregulatory control of GFR).

5.2 Oncotic Pressure in Glomerular Capillaries (π_{GC})

This is the main force that opposes filtration. Also, as fluid is filtered, onotic pressure increases within the capillaries, decreasing GFR. This increase in oncotic pressure is minimized as flow increases. Thus, an increase in renal blood can in itself increase GFR. The increased plasma protein concentration leaving the glomerular capillaries passes downstream into the peritubular capillaries increasing the force of reabsorption.



▲ **Figure 24–5.2** Glomerular Capillary Forces

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5.3 Hydrostatic Pressure in Bowman Space (P_{BS})

Hydrostatic pressure in the Bowman space opposes filtration. Normally low and insignificant and does not affect GFR. Urinary tract obstruction raises pressure in Bowman space and decreases GFR (postrenal failure).

5.4 Oncotic Pressure in Bowman Space (π_{BS})

This force promoting filtration is considered insignificant and close to zero.

Normal values:

P_{GC} = 55 mmHg P_{BS} = 18 mmHg
π_{GC} = 27 mmHg π_{BS} = 0 mmHg

Net filtration pressure =
$(P_{GC} + \pi_{BS}) - (P_{BS} + \pi_{GC})$ = 10 mmHg

GFR = K × Net filtration pressure

K = Filtration coefficient. This is determined mainly by capillary permeability and surface area.

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6 Overall Flow Distribution Within the Kidney

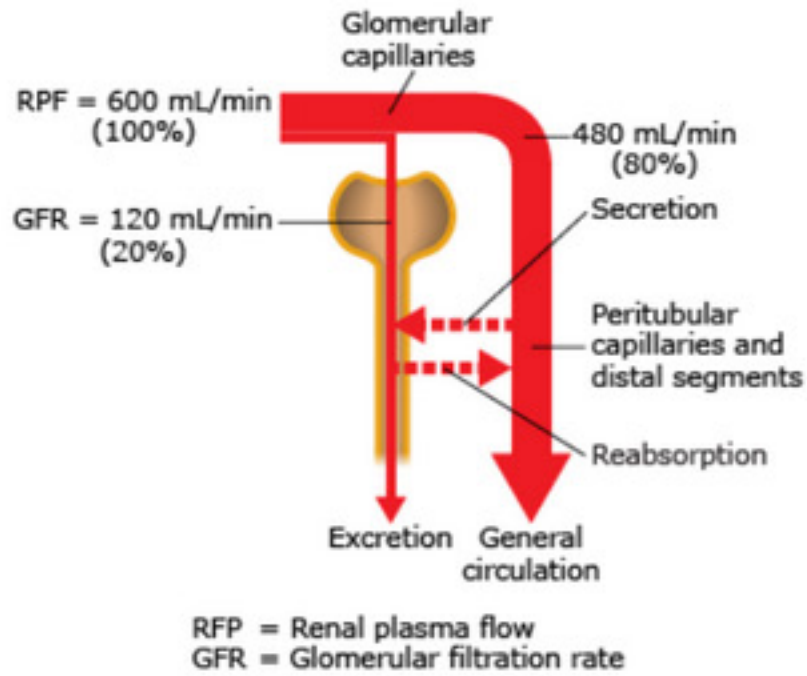
Filtration Fraction (FF) is the fraction of the plasma entering the kidney that is filtered usually expressed as a percentage. It also represents the percentage filtered for any substance freely filtered.

$$FF = \frac{GFR}{RPF} \qquad GFR = 120 \text{ mL/min} \quad RPF = 600 \text{ mL/min}$$

$$= \frac{120}{600}$$

$$= .20 \text{ or } 20\%$$

The main factor determining FF is renal plasma flow. As the flow decreases, the plasma spends more time within the glomerular capillaries which *tends* to increase filtration fraction. It is just a tendency and many clinical situations often do not show this tendency.



▲ **Figure 24–6.0** Overall Flow and Transport in the Kidney

6.1 Effects of Sympathetic Innervation

Sympathetic neurons innervate the afferent and efferent arterioles. Increased activity constricts, but the main effect is on the afferent.

Overall: ↓ RPF
↓ GFR
↑ FF
↑ Force of reabsorption in the peritubular capillaries ↓ hydrostatic pressure, but ↑ plasma oncotic pressure due to increased FF.

The net effect is, less is filtered but a greater percentage of the filtrate is reabsorbed. Fluid and electrolytes are conserved.

6.2 Effects of Angotensin II

Angiotensin II is a very potent vasoconstrictor and has a major role in maintaining blood pressure. In the kidney, it has a more pronounced constrictor action on the efferent arteriole. In the setting of a mild to moderate drop in blood pressure, the relative selective constriction of the efferent arteriole by angiotensin II, helps maintain P_{GC} and GFR. Likewise, an *ACE inhibitor* or an *angiotensin blocker* preferentially dilates the efferent arteriole potentially reducing P_{GC} and GFR.

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7 Filtered Load

- GFR is the rate at which fluid is filtered (e.g., mL/min).
- Filtered load is the rate at which a substance is filtered (e.g., mg/min).

Filtered Load = GFR x P_x

GFR units = volume/time (e.g., mL/min)

P_x units = amount/volume (e.g., mg/mL)

This equation is only valid for a freely filtered substance.

Using the following information calculate the filtered load of each substance:

GFR = 120 mL/min

Plasma sodium = 140 mEq/L

Plasma glucose = 100 mg/dL

Plasma PAH = 3 mg/mL

Answers: sodium = 16.8 mEq/min;
glucose = 120 mg/min
PAH = 360 mg/min.

Note: In preforming the calculation, the volume units must match then they cancel.

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CHAPTER 25

Renal Function and the Concept of Clearance

1 General Concepts

1.1 Renal Clearance

Renal clearance is a theoretical volume of plasma from which a substance is removed and excreted in the urine. Consider the following:

- If a substance has a plasma concentration of 2mg/mL, and 2 mg is excreted in the urine over a period of 1min, the volume cleared is 1 mL/min.
- If 4mg is excreted per minute, the cleared volume is 2mL/min.
- If the plasma concentration increases to 4mg/mL, and 4mg is excreted per minute we are back to a clearance of 1mL/min.

Thus, the cleared volume depends on the amount excreted per unit time and the plasma concentration.

$$\text{Clearance of x} = \frac{\text{Excretion of x}}{Px} = \frac{Ux \times V}{Px}$$

Ux = urine concentration of x (amount/volume)

V = urine flow (volume/time)

Px = plasma concentration of x (amount/volume)

Note: The urine and plasma concentration units must match in order to cancel. The units for V become the units for clearance (volume/time).

From the following information calculate the clearances of glucose:

V = 4 mL/min

$P_{glucose}$ =100 mg/100mL

U glucoses of: 0 mg/mL, 1mg/mL, 2mg/mL

Answers: 0 mL/min; 4mL/min; 8mL/min

1.2 Clearance as an Index of GFR and Renal Function

GFR is considered the clinical index of renal function. Renal failure is a failure in GFR. Acute renal failure is a fairly sudden loss of GFR and, in most cases, is potentially reversible. Chronic renal failure involves a loss of functioning nephrons and, thus, is not reversible.

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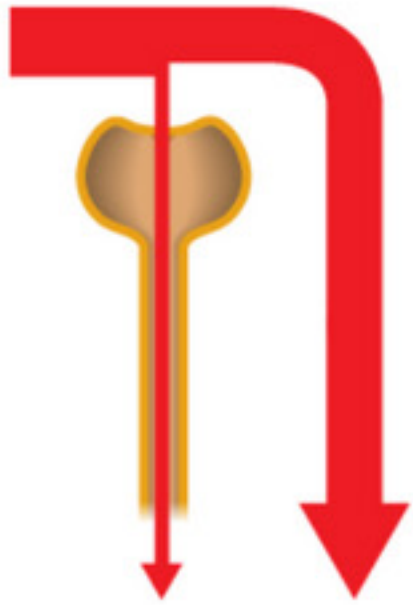
The clearance of a substance can be used as an index of GFR and renal function if:

- It is freely filtered.
- Not reabsorbed, secreted, or metabolized by the kidney.

Substances include inulin, mannitol, and sucrose. Even though the clearance of any of these substances would provide a gold standard for GFR, they are not used clinically. Instead, the plasma level of creatinine is the clinical index of GFR.



▲ **Figure 25-1.2A** Clearance of GFR and Renal Function

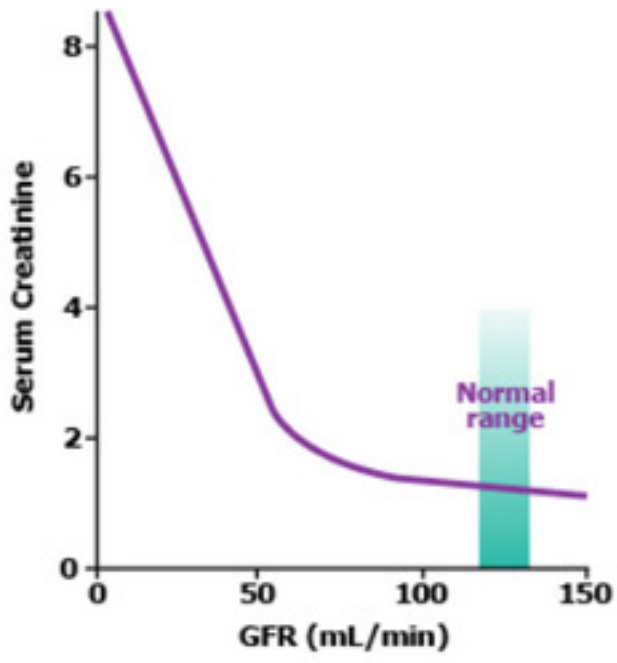
1.2.1 Creatine: The Basics

- Breakdown product of skeletal muscle.
- Constant release into the circulation in proportion to muscle mass.
- Freely filtered, not reabsorbed, slightly secreted.

Assuming creatinine production remains constant:

- An increase in GFR increases the excretion of creatinine decreasing the plasma concentration.
- A decrease in GFR decreases the excretion of creatinine and raises the plasma concentration.

Even though it is the clinical standard, the plasma level of creatinine is not a sensitive index of GFR. It will only demonstrate large changes in GFR. With muscle injury, plasma creatinine is elevated and not an index of GFR.



▲ **Figure 25–1.2B** Plasma Creatinine vs. GFR

The only accurate estimate of GFR is the calculated clearance of creatinine. All that is needed is the following:

- Plasma creatinine concentration.
- Timed urine collection and urine concentration of creatinine.

This is rarely performed in the clinical setting.

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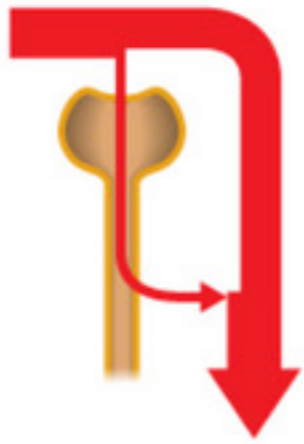
2 Renal Transport and Clearance

2.1 Filtered Substances and Complete Reabsorption

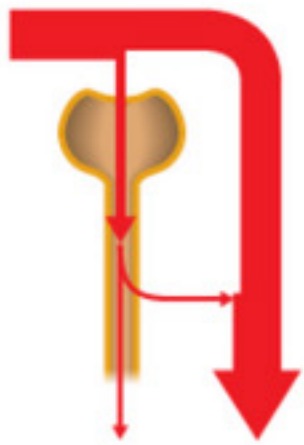
Substances freely filtered and completely reabsorbed or not filtered. Clearance = 0. If the substance does not appear in the urine, its renal clearance is zero (e.g., glucose, amino acids, protein). For a substance to have a positive clearance, it must appear in the urine. Once glucose exceeds its renal threshold, it appears in the urine and, thus, a positive clearance.



▲ **Figure 25-2.1** Filtered Substances and Complete Reabsorption

2.2 Filtered Substances and Partial Reabsorption

Substances freely filtered and partially reabsorbed. Clearance >0< GFR (e.g., sodium, urea, potassium). Almost all of the filtered sodium is reabsorbed, but sodium cannot be completely reabsorbed. It is always present in the urine. Thus, sodium always has a positive clearance, but it is just above zero. An osmotic diuresis *increases* the clearance of sodium, but an increase in aldosterone *decreases* the clearance of sodium. Urea is freely filtered and partially reabsorbed. Like sodium, it always appears in the urine and has a positive clearance. However, urea reabsorption follows water reabsorption though not proportionately. Thus, a diuresis increases the clearance of urea and decreases its plasma concentration whereas an antidiuresis decreases the clearance of urea and increases its plasma concentration. Potassium reabsorption in the proximal tubule is normally greater than its secretion in the collecting duct and has a clearance less than GFR.



▲ **Figure 25–2.2** Filtered Substances and Partial Reabsorption

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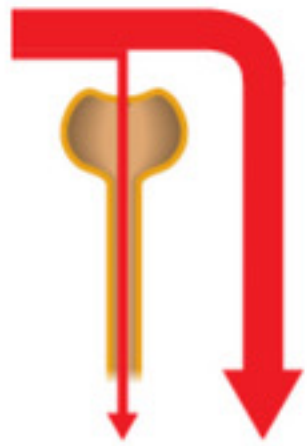
2.3 Filtered Substances and No Net Tubular Transport

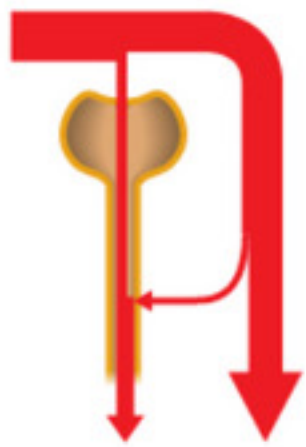
Substances freely filtered and no net tubular transport. Clearance = GFR (e.g., inulin, sucrose, and mannitol). Regardless of the plasma concentration, the clearance would always equal GFR. Also, if a substance is freely filtered and normally completely or partially reabsorbed, and the reabsorption was completely inhibited, its clearance would also equal GFR. If substance X completely inhibited the reabsorption of glucose in the proximal tubule, then the clearance of glucose would be an ideal index of GFR.



▲ **Figure 25–2.3** Filtered Substances and No Net Tubular Transport

2.4 Substances Filtered and Partially Secreted

Substance freely filtered and partially secreted. Clearance > GFR < RPF (e.g., Creatinine). If freely filtered, and what is filtered is excreted, and if there is some net secretion, its clearance must be greater than GFR. At a given plasma level the more that is secreted the higher the clearance rises above GFR.



▲ **Figure 25–2.4** Substances Filtered and Partially Secreted

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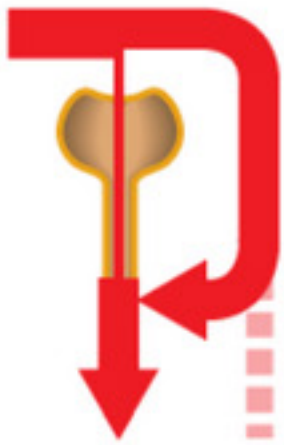
2.5 Substances Freely Filtered and Completely Secreted

Substance is freely filtered and complete secreted. Clearance = RPF. Under these conditions, the substance would not be present in the renal venous blood. If a substance enters the kidney, but does not appear in the renal venous blood, its clearance would equal renal plasma flow. If it does appear in the renal venous blood, it has a clearance less than renal plasma flow. Renal plasma flow is theoretically the greatest kidney clearance possible. However, a calculated clearance could in some cases be greater than renal plasma flow. This would mean the substance is manufactured by the kidney and excreted in the urine (e.g., ammonium).



▲ **Figure 25-2.5** Substances Freely Filtered and Completely Secreted

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3 Concept of Free Water and Free Water Clearance

- Free water is solute-free (i.e., sodium-free) water.
- Free water is created when Na is separated from water.
- An example is fluid in the ascending limb of the loop of Henle. Electrolytes are reabsorbed, but water is not.

Free water clearance is the balance between solute and water excretion.

- CH_2O (0): isotonic urine. Equal proportions of solutes and water are lost. No change in plasma osmolarity. No gain or loss of free water.
- CH_2O (+): hypotonic urine. Water is excreted in excess of solutes. Plasma osmolarity increases. Individual loses free water.
- CH_2O (−): hypertonic urine. Solutes are excreted in excess of water. Plasma osmolarity decreases. Individual gains free water.

Free water clearance is used to determine if the kidneys are responding in an appropriate manner to maintain a normal body osmolarity. Hypernatremia should be associated with negative free water clearance and hyponatremia with a positive free water clearance.

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CHAPTER 26 Dynamics of Renal Transport: Reabsorption and Secretion

1 Reabsorption

Reabsorption along the nephron segment can be active or passive. Active reabsorption involves a protein carrier and is powered by ATP. The substance is moved against its electrical-chemical gradient. Active reabsorption can be divided into two basic types based on the observed dynamics of the reabsorption. T_m systems have a transport maximum (i.e., with increased load the reabsorption rate increases until the transport carriers are saturated). At that point the reabsorption rate is at a maximum (T_M). An example is the proximal tubular reabsorption of glucose. In some cases, factors other than the maximum rate of carrier transport determines the maximum rate of reabsorption. An example to consider is the proximal tubule reabsorption of sodium. The maximal reabsorption rate of sodium is below the capacity to pump sodium because some of the sodium actively reabsorbed leaks back into the proximal tubule. In this case, the maximum reabsorption rate depends on the gradient across the membrane and the time spent in the proximal tubule (gradient time system).

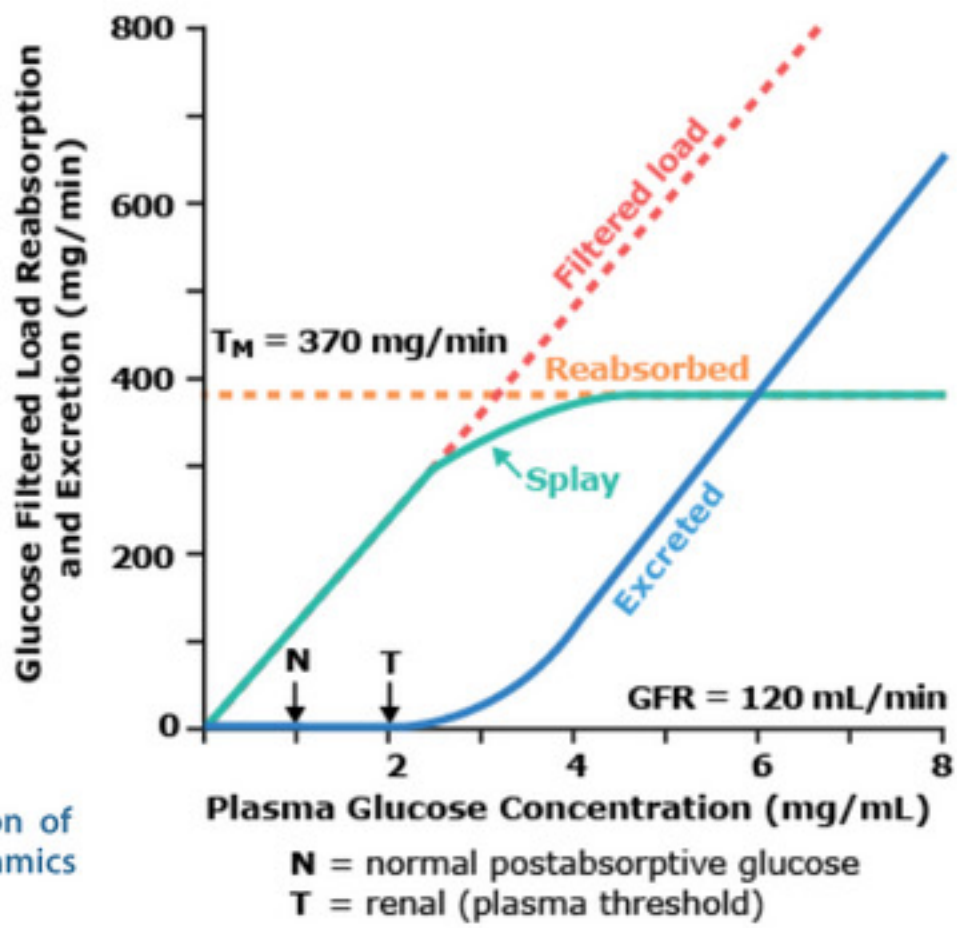
1.1 Transport Maximum Systems

An example is the reabsorption of glucose in the proximal tubule.

General Dynamics of the system:

- Exhibits saturation kinetics
- Transporters have a high affinity for substrate
- Back leak is minimal or absent

Back leak is the same as *back diffusion*. It is the diffusion of the substance once released into the interstitum back into the tubule lumen. Back leak does not occur because the tubular membrane system is impermeable to the substrate. Overall, the filtered load is completely reabsorbed until the carriers are saturated. Remaining substrate is excreted.



▶ **Figure 26–1.1** Relationships Among Filtered Load, Reabsorption, and Excretion of Glucose in the Proximal Tubule. The Dynamics of a T_M System.

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- At low filtered loads below carrier saturation, filtration rate = reabsorption rate and urine glucose is zero.
- Glucose appears in the urine when, in some nephrons, the carriers become saturated. The plasma level of glucose where this occurs is referred to as *renal (plasma) threshold*.
- The curving of the reabsorption line into the plateau (called *splay*) is because not all nephrons are saturated at the same filtered load. At the beginning of splay some nephrons are saturated. As splay continues more and more nephrons become saturated. T_m is not reached until the plateau where all nephrons are saturated.
- Threshold is the plasma level at which glucose appears in the urine (beginning of splay) T_M is the rate of reabsorption when all the carriers are saturated (beyond splay on the plateau).
- T_M dynamics is exhibited by all natural organic substances reabsorbed in the proximal tubule except urea. Urea is partially reabsorbed but passively. Urea tends to follow the water but not proportionately.
- T_M dynamics is also exhibited in the proximal tubule by some inorganic ions (e.g., phosphate and calcium).

1.2 Gradient Time System

General Dynamics of the System:

- Carriers are always operating below capacity (never saturated)
- Affinity for the substrate is low
- High back leak

Some of the sodium reabsorbed leaks back into the tubule lumen. This is because the proximal tubule has leaky tight junctions to sodium. The system is also leaky to potassium, chloride and water. In a gradient-time system, the slower the flow the greater the percentage of the filtrate reabsorbed. It can be up to three-quarters of the filtered load, but under normal conditions it is about two-thirds and does not fall much below this value. This means that as the filtered load increases the reabsorption rate of sodium (mg/min) increases. This minimizes an increased delivery of sodium to distal segments when the filtered load increases. This is referred to as glomerulotubular balance.

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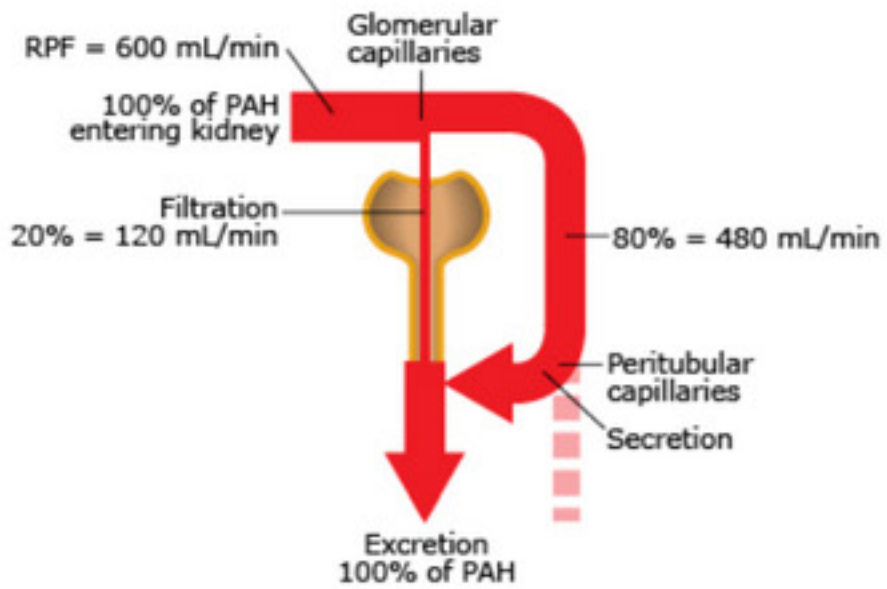
2 Secretion

The proximal tubule is an important site for the secretion of organic substances. Many waste products (e.g., bile salts, urate) and non-natural organic substances (e.g., para-aminohippuric acid, or PAH, and penicillin are rapidly cleared by active secretion into the proximal tubule). It is a fairly nonspecific transport system that exhibits T_m dynamics. The following shows the dynamics for PAH. PAH is freely filtered, actively secreted, but cannot be reabsorbed.



▲ **Figure 26–2.0** Dynamics of PAH: Filtration Plus Secretion

- The entire filtered load of PAH is excreted; thus, the GFR is always cleared of PAH.
- The plasma flow to the peritubular capillaries is entirely cleared at low plasma concentrations of PAH (carriers not saturated).
- At low plasma levels of PAH clearance is renal plasma flow and no PAH appears in the renal venous blood.
- When the carriers are saturated, some of the plasma delivered to the peritubular capillaries is not cleared of PAH. Clearance is below renal plasma flow and some PAH appears in the renal venous blood.
- At very high plasma concentrations of PAH, only a small fraction of the plasma delivered to the peritubular capillaries is cleared of PAH. Clearance is now slightly above GFR.
- At low plasma levels, the clearance of PAH is a good index of renal plasma flow. At high plasma levels, its clearance is a good index of GFR.

The calculated clearance of PAH is often stated to be effective renal plasma flow (i.e., flow delivered to the nephron system). About 10% of renal plasma flow perfuses the fibrous capsule. This is not cleared of PAH. Thus, the true renal plasma flow is about 660 mL/min.

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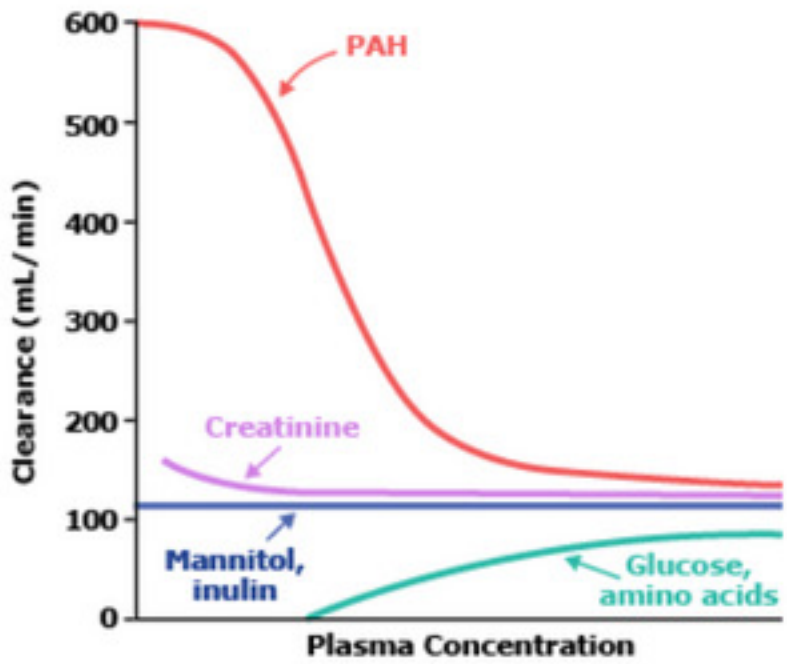
3 Graphical Representation of the Clearance of Some Substance Types

Only those substances whose clearance can be easily related to their plasma level are shown. For example, sodium's clearance is not a function of its plasma concentration and cannot be depicted as a curve on the graph. Also, data presented is at a renal plasma flow of 600 mL/min and a GFR of 120 mL/min.



▲ **Figure 26–3.0** Graphical Representation of the Clearance of Some Substance Types

3.1 Mannitol, Inulin

Because its line is parallel to the X-axis, the clearance of inulin is independent of its plasma concentration. As the plasma levels rise the filtered load and the excretion rise but the volume cleared remains at GFR. If GFR increases the curve shifts upward. If GFR decreases the curve shifts downward.

3.2 Glucose, Amino Acids

At low plasma levels there is no glucose in the urine and clearance is zero. The curve begins where glucose first appears in the urine. That plasma level on the X-axis by definition is renal threshold. As the plasma level rises further, a smaller proportion of the filtered glucose is reabsorbed and clearance increases. Its clearance will approach that of inulin, but never equal inulin and GFR as long some glucose is reabsorbed.

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3.3 PAH

At low plasma concentrations PAH is cleared from the 120 mL/min filtered and the 480 mL/min delivered to the peritubular capillaries. As such, the venous plasma concentration is zero. As the curve dips down clearance is less than renal plasma flow. At this point some of the PAH in the 480 mL/min delivered to the peritubular capillaries is not secreted. In some nephrons, the transport carriers are saturated and PAH is present in the renal venous blood. As the plasma level goes higher, a smaller proportion delivered to the peritubular capillaries is secreted. Clearance decreases further and approaches GFR. If secretion of PAH was completely inhibited, no matter what the plasma concentration, its clearance would equal GFR.

3.4 Creatinine

Since creatinine exhibits some net secretion, its clearance is always slightly greater than GFR. But note that despite large variation in the plasma level its clearance remains close to GFR.

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4 Net Transport in the Nephron

Net transport in the nephron is found by comparing the rate at which the substance enters the system, filtered load, with the rate at which it leaves the system in the urine, excretion.

Filtered load amount/time mg/min	=	GFR volume/time mL/min	×	P_X amount/volume mg/mL
Excretion amount/time mg/min	=	U_X amount/volume mg/mL	×	V volume/time mL/min

GFR = glomerular filtration rate
P_X = plasma concentration

U_X = urine concentration
V = urine flow rate

▲ **Figure 26–4.0** Net Transport in the Nephron

There are three completely different situations to evaluate.

4.1 Substances Freely Filtered but No Tubular Modification

- No net reabsorption or secretion.
- Filtration rate must always equal the excretion rate.
- Clearance equals GFR.
- Inulin, mannitol, sucrose.

4.2 Substances Freely Filtered and Net Reabsorption

- Filtered load always greater than excretion.
- If completely reabsorbed, filtration rate equals reabsorption rate.
- Reabsorption rate = filtration rate − excretion rate.
- Clearance always less than GFR.
- Glucose, sodium, potassium, urea.

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4.3 Substances Freely Filtered and Net Secretion

- Excretion always greater than the filtered load.
- Secretion = excretion rate − filtered load.
- Clearance always greater than GFR.
- PAH, creatinine.

The standard formula for calculating net transport is as follows:

$$\text{Net transport} = (\text{GFR} \times P_c) - (U_c - V)$$

P_c = Plasma concentration

U_c = Urine concentration

0 = No net transport of the substance

+ = Net reabsorption of the substance

− = Net secretion of the substance

4.4 Pictorial Depictions of Net Transport

The assumption is that the person is on a western diet (including red meat) and is in antidiuresis. The thick solid lines approximate quantitation. In all cases, the substance is freely filtered (20%) and thus, 80% is delivered to the peritubular capallaries.

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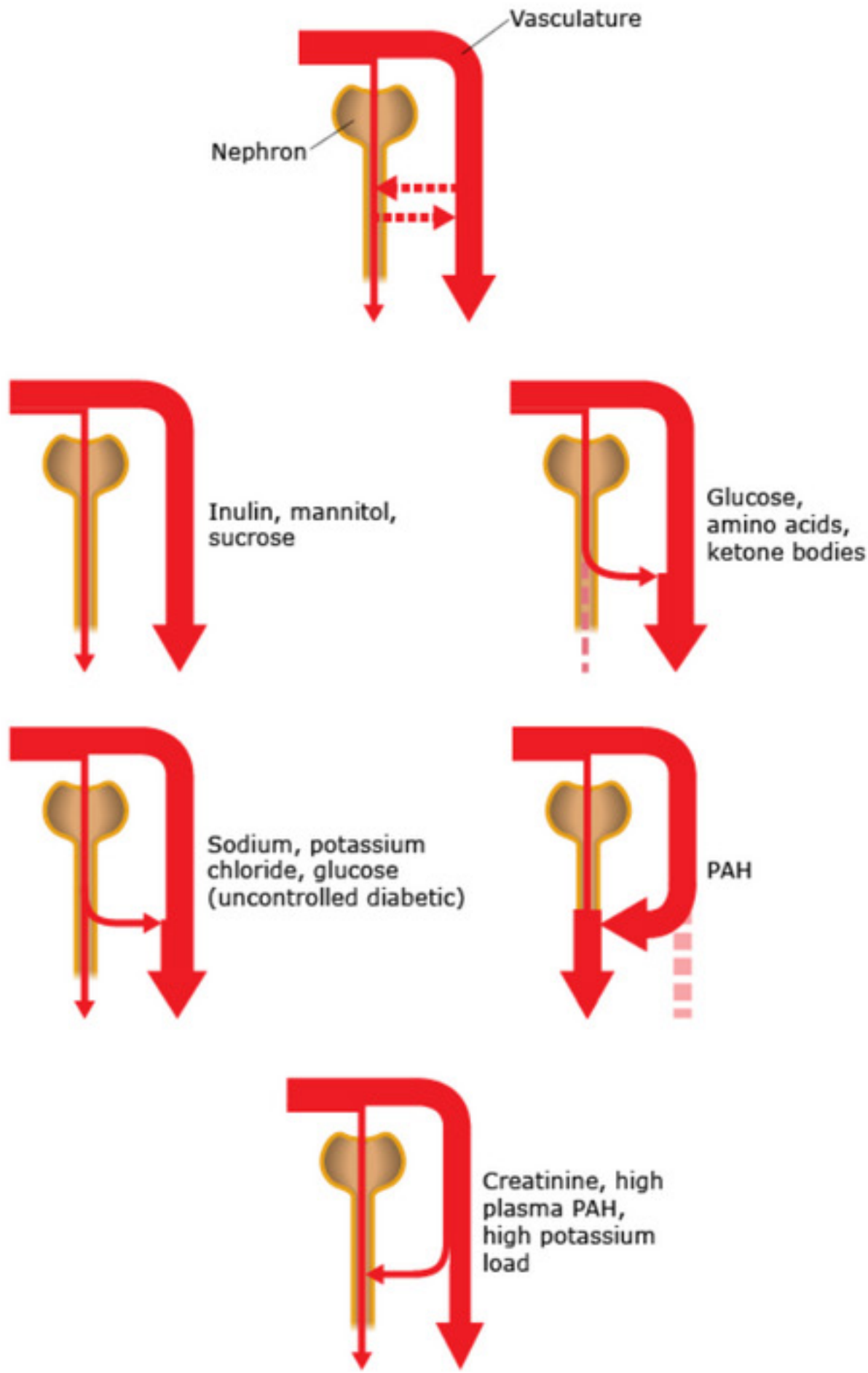

▲ **Figure 26–4.4** Net Transport of Type Substances

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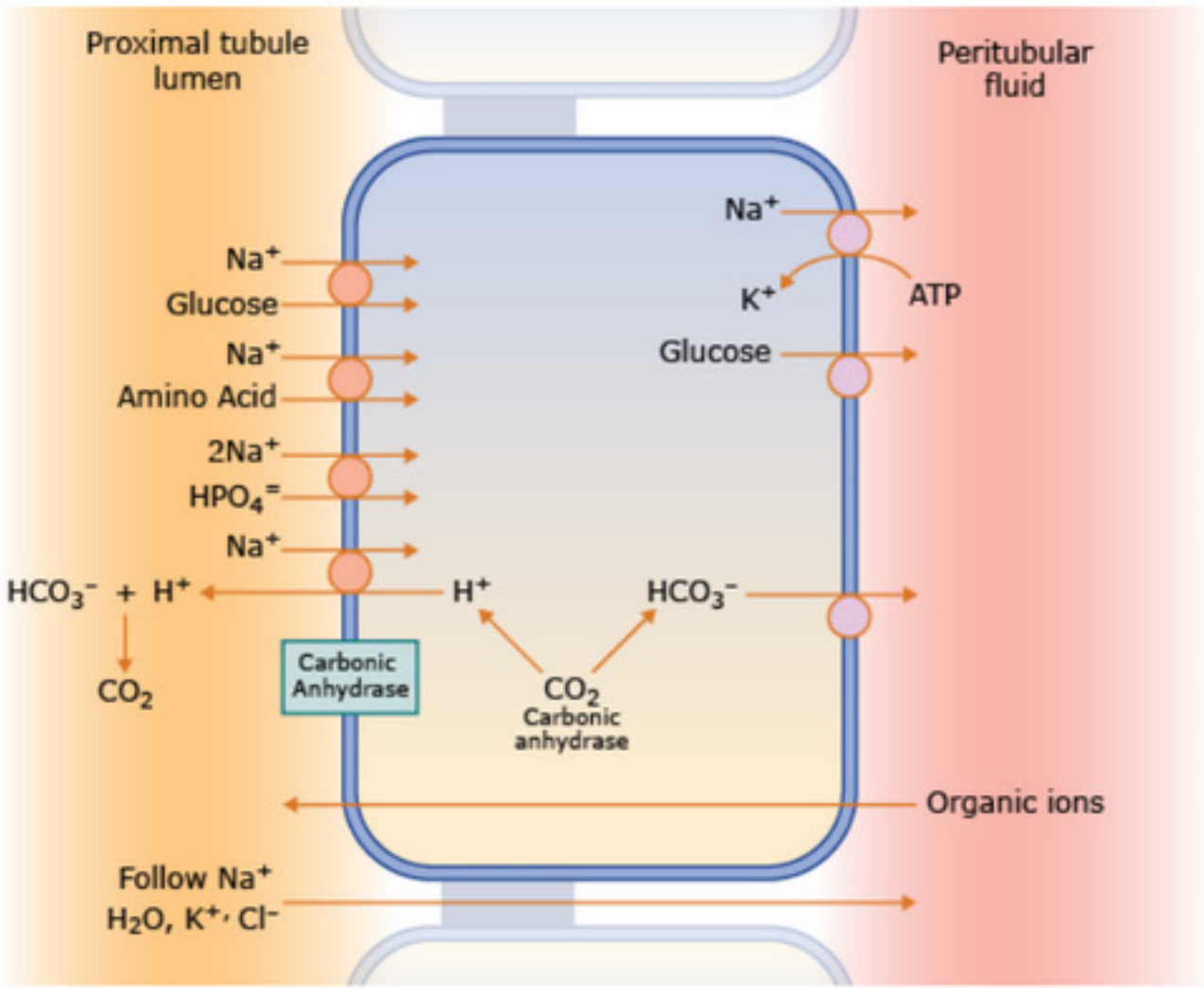
1 Proximal Tubule

The fluid delivered to the proximal tubule from Bowman space is the isotonic GFR, (120 mL/min). Thus, osmolarity is close to 300 mOsm and the concentration of any freely filtered substance is the same as the plasma concentration. The following figure is a summary of all the transport processes along the length of the proximal tubule.



▲ **Figure 27–1.0** Proximal Tubule Transport

1.1 Electrolyte and Water Transport

- Two thirds of the filtered sodium is reabsorbed via active transport, primary and secondary.
- Two thirds of the filtered water and potassium follow the sodium (leaky tight junctions). Because equal proportions of sodium, potassium and water are reabsorbed, their concentrations do not change along the length of the proximal tubule. Osmolarity remains at 300 mOsm.
- 80 to 90% of the filtered bicarbonate is reabsorbed by an indirect mechanism.

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- Because greater than two thirds of the bicarbonate is reabsorbed, less than two thirds of the chloride is reabsorbed to maintain electrical neutrality. Bicarbonate concentration decreases and chloride concentration increases along the length of the proximal tubule.

1.2 Metabolites

- Most metabolites are completely reabsorbed in this segment via secondary active transport. This includes: glucose, ketone bodies, peptides, and amino acids. Concentration at the end of the proximal tubule is zero.
- Urea is partially passively reabsorbed. Urea tends to follow the water, but not proportionately.

1.3 Secretion

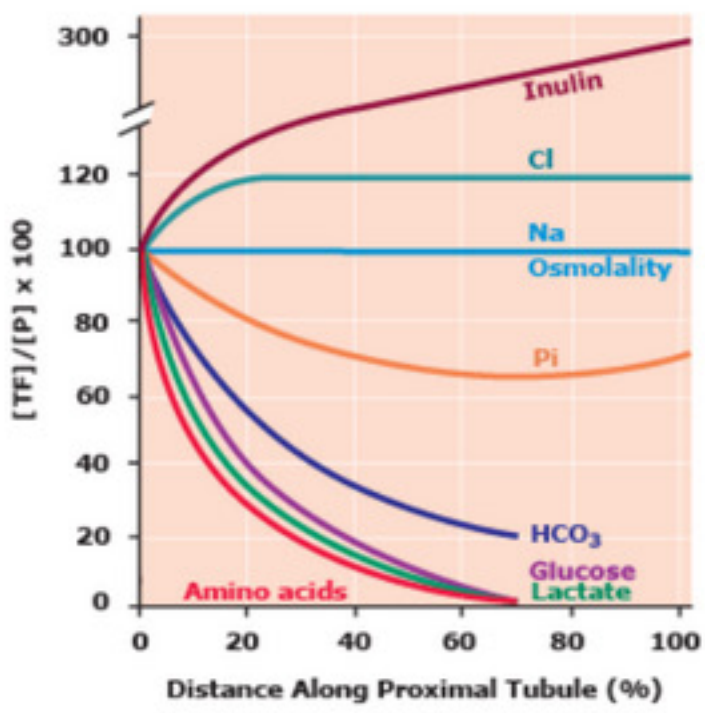
- Active secretion of the metabolites, creatinine, urate and many nonnatural substances (PAH, penicillin, etc.).

Summary: approximate two thirds of the major electrolytes and water is reabsorbed as well as complete reabsorption of many metabolites. Osmolarity has not changed but the volume has been reduced from 120 mL each minute to 40 mL per minute.

1.4 Energy Balance

- All substances reabsorbed in the proximal tubule depend directly or indirectly on the Na/K-ATPase pump. Complete inhibition of the Na/K-ATPase pump means nothing is reabsorbed in the proximal tubule. Since most of what is filtered is reabsorbed in the proximal tubule the Na/K-ATPase pump is the most energy-demanding process of the nephron. Thus, the metabolic rate of the kidney is proportional to the sodium reabsorption in this segment. Since GFR determines the filtered load of sodium and its reabsorption rate in the proximal tubule, the metabolic rate is also proportional to GFR.

1.5 Graphical Representation of Proximal Tubule Reabsorption



▲ **Figure 27-1.5** Graphical Representation of Concentration Changes Along the Proximal Tubule

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1.6 Diuretics

- The proximal tubule is the main site of action of osmotic diuretics (e.g., carbonic anhydrase inhibitors, mannitol). These agents decrease water reabsorption and, as a consequence, there is a greater back diffusion of electrolytes and an increase in the excretion of water, Na, K, Cl and with carbonic anhydrase inhibitors bicarbonate. Since more water than electrolytes are lost, they can promote a hypernatremia. The same effect is achieved if there is incomplete glucose reabsorption in the proximal tubule.

1.7 Pathophysiology

1.7.1 Fanconi Syndrome

- Generalized dysfunction of proximal tubule cells of unclear cause.
- Likely due to a defect in cellular energy metabolism resulting in multiple transport abnormalities.
- Results in impaired reabsorption of multiple substances, including glucose, amino acids, phosphate, and bicarbonate.

Cause:

- Idiopathic
- Drug toxicity
- Multiple myeloma (light chain toxicity)
- Inherited disorders:
  - The most common is *cystinosis*, a rare disorder of cysteine deposition in tissues.

Clinical Manifestations:

- Urinary solute loss leads to osmotic diuresis: polyuria, polydipsia, and dehydration.
- Multiple metabolic abnormalities:
  - Impaired reabsorption of phosphate and bicarbonate directly leads to: (1) metabolic acidosis—type II renal tubular acidosis, and, (2) hypophosphatemia.
  - Indirect effects: osmotic diuresis → increased distal Na^+ delivery → distal K^+ and Ca^{++} loss → secondary (3) hypokalemia and (4) hypocalcemia
- Major complication: abnormal bone formation with resultant growth impairment and failure to thrive.
  - The bone defects (i.e., rickets or osteomalacia) result from acidosis, hypophosphatemia, and hypocalcemia.

1.7.2 Renal Tubular Acidosis Type II

- Caused by a decreased capacity to reabsorb the filtered load of bicarbonate in the proximal tubule.
- Initially, bicarbonate lost in the urine until the filtered load decreases to equal the new diminished capacity.
- Chronic metabolic acidosis with decreased plasma bicarbonate and an acid urine.

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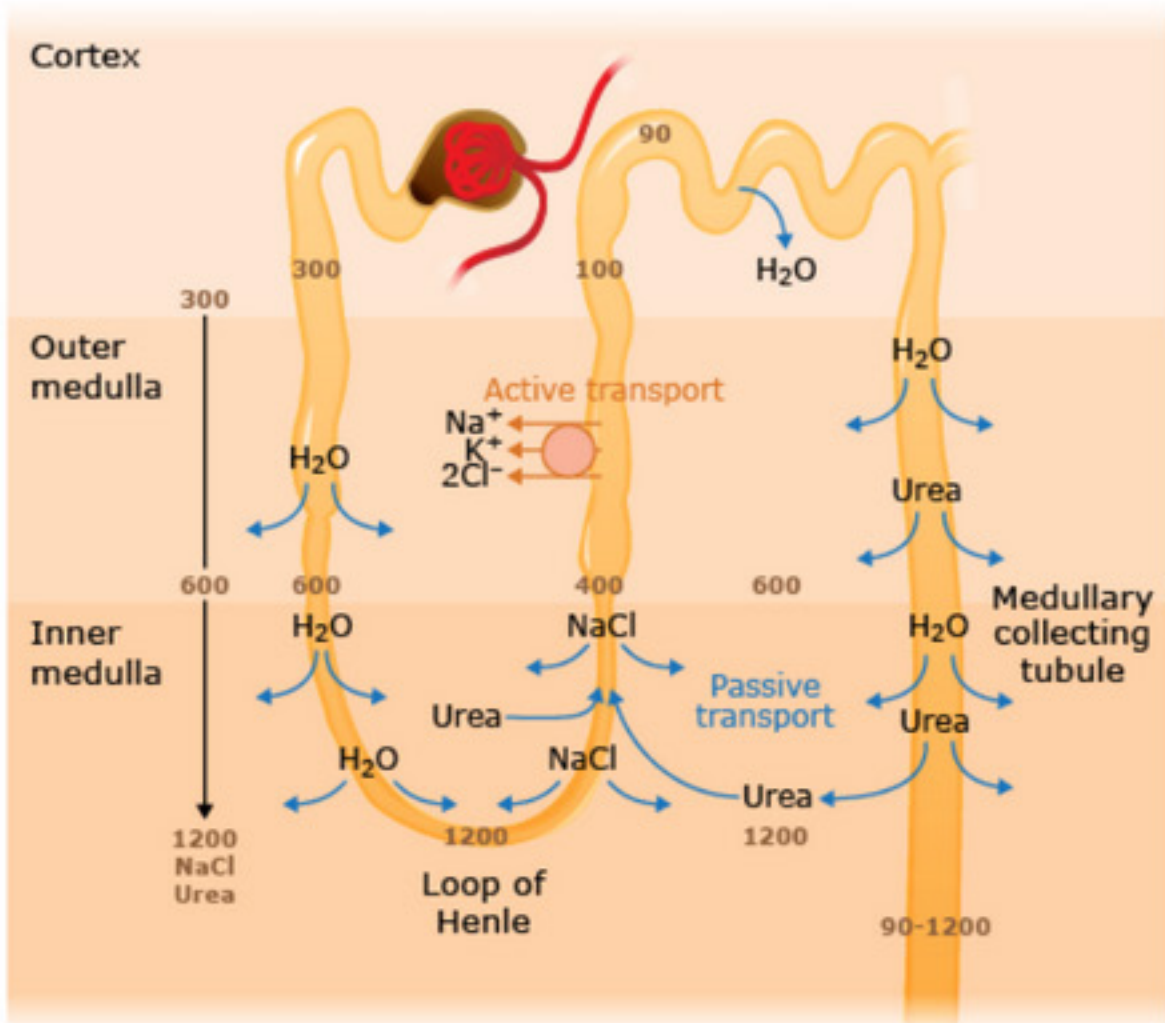
2 Loop of Henle

Receives the isotonic fluid delivered from the proximal tubule which has been reduced to one third of the original volume. The loop of Henle has three main functions:

- It continues the reabsorption of water and electrolytes. Up to about 25% of the filtered electrolytes are reabsorbed in this segment.
- It acts as a *countercurrent multiplier*, which creates an osmolar gradient within the medullary interstitium. This gradient allows ADH acting on the collecting duct to concentrate the urine. In order for the countercurrent multiplier to maintain this gradient there must be a fairly low flow through the system. High flow reduces the interstitial gradient and ADH is unable to form a concentrated urine. In other words, if the proximal tubule does not do its job and the loop flow is too high as occurs in an uncontrolled diabetic a dilute urine will be formed.
- It must reabsorb more electrolytes than water and deliver a hypotonic fluid to the distal tubule.



▲ **Figure 27–2.0A** Loop of Henle Countercurrent Multiplier

In order to carry out its functions as a countercurrent multiplier, the loop of Henle must have specific functional characteristics:

First: A countercurrent flow (descending and ascending limb).

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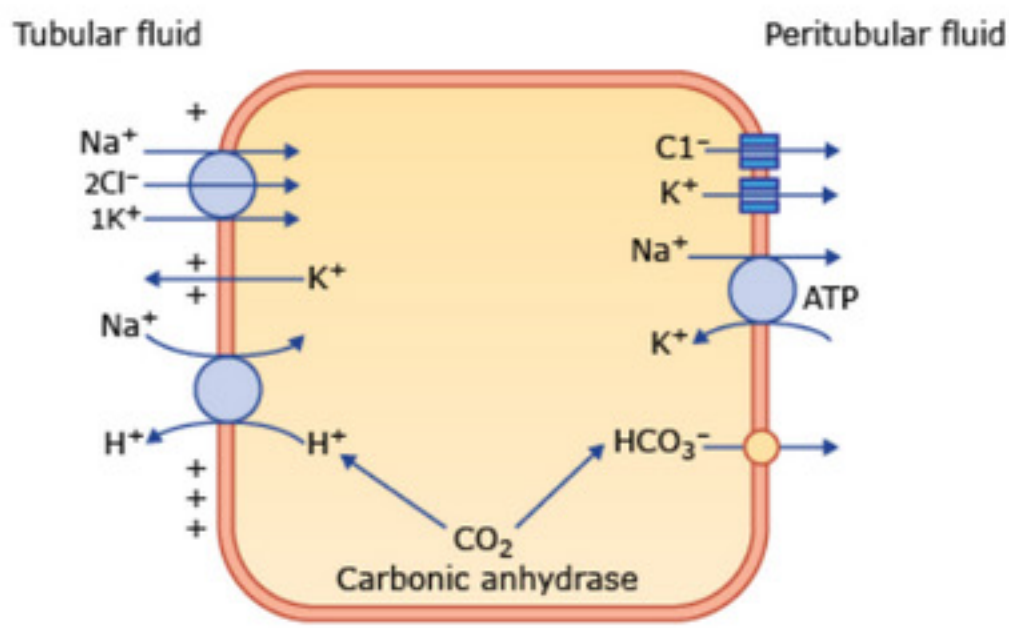
Second: The descending limb must be permeable to water. Water diffuses into the hyperosmotic interstitium and osmolarity increases down the descending limb. Equilibrium will occur with the interstitium and the osmolarity at the tip of the loop of Henle is the highest of any nephron segment. At the end of the collecting duct the osmolarity can equal this value but only with the maximum effect of ADH.

Third: Electrolytes but not water must be reabsorbered by the ascending limb. The ascending limb is impermeable to water. Electrolytes are absorbed passively in the thin ascending limb, drawn out by urea which in this segment acts as an osmotic agent, and actively in the thick ascending limb. Because osmolarility decreases in the ascending limb, it is referred to as the *diluting segment* of the nephron. In fact, the fluid leaving the loop is *hypotonic*.

Fourth: As mentioned earlier, slow flow is required. This also applies to the vasa recta, capillary loops that have a countercurrent flow within the medullary interstitium. They remove the water and electrolytes reabsorbed here without disrupting the interstitial osmolar gradient.

In summary, the loop of Henle reabsorbs about 25% of the filtered electrolytes and 15% of the filtered water. Like the proximal tubule it is powered by the Na/K-ATPase pump on the basolateral membrane of the thick ascending limb as shown in the following figure.



▲ **Figure 27–2.0B** Transport Thick Ascending Limb

On the luminal membrane the Na, K, and Cl enter via a protein mediated but passive process. This is an electro-neutral event; however, some of the potassium diffuses back down its electrochemical gradient into the tubule lumen creating the net positive charge. The positive luminal charge facilitates the reabsorption of the divalent calcium and magnesium via a paracellular pathway.

2.1 Diuretics

Loop diuretics (furosemide) selectively inhibit the Na/K/2Cl cotranporter and reduce the positive luminal charge increasing the excretion of calcium and magnesium as well as the major electrolytes. These are powerful diuretics much more so than those that act on the distal tubule (thiazides).

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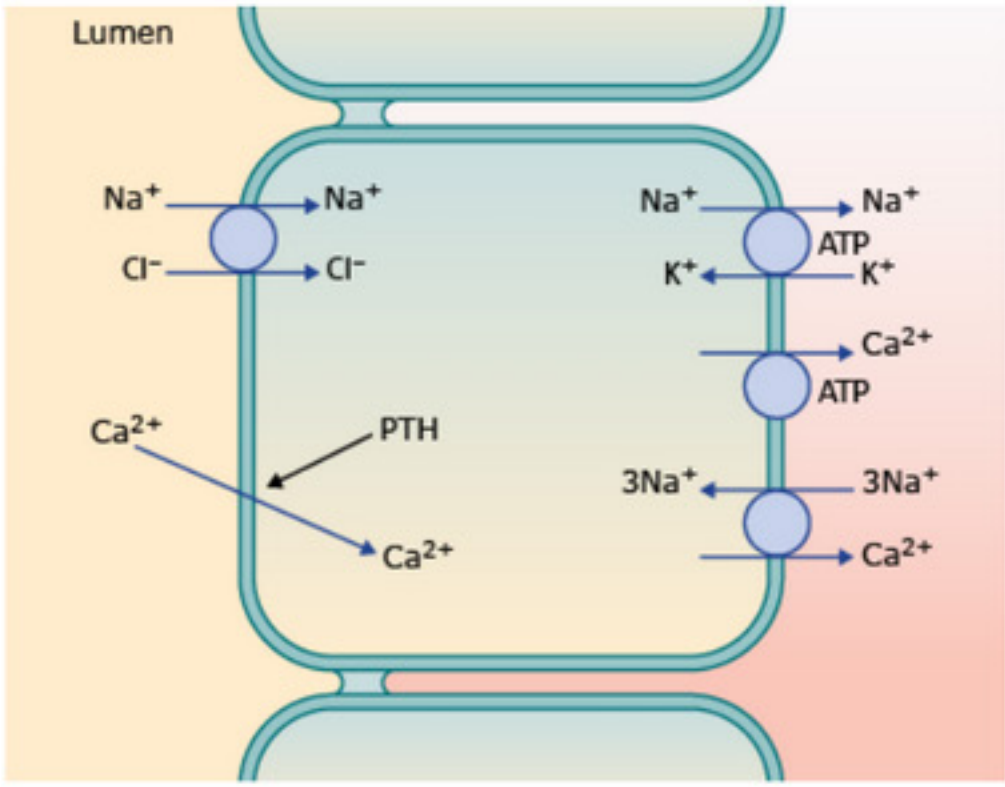
3 Early Distal Tube

The early distal tubule is similar to the ascending limb of Henle in that Na and Cl continue to be reabsorbed without water, further reducing the tubule osmolarity. Na and Cl enter the cell via an electrically neutral cotransporter. Because there is no recycling of K, there is no positive luminal charge in this segment. Ca continues to be reabsorbed, passively across the luminal membrane but actively across the basal membrane by two mechanisms. The process is regulated by parathyroid hormone. Only about 10% of the filtered NaCl is reabsorbed in this segment.



▲ **Figure 27–3.0** Distal Tubule Transport

3.1 Diuretics

Thiazide diuretics inhibit the NaCl cotransporter mainly in the distal tubule. Unlike loop diuretics which inhibit Ca reabsorption, thiazides enhance Ca reabsorption. They are less powerful diuretics than loop diuretics, since less NaCl is reabsorbed in this segment (10% versus 25%).

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4 Late Distal Tubule and Collecting Duct

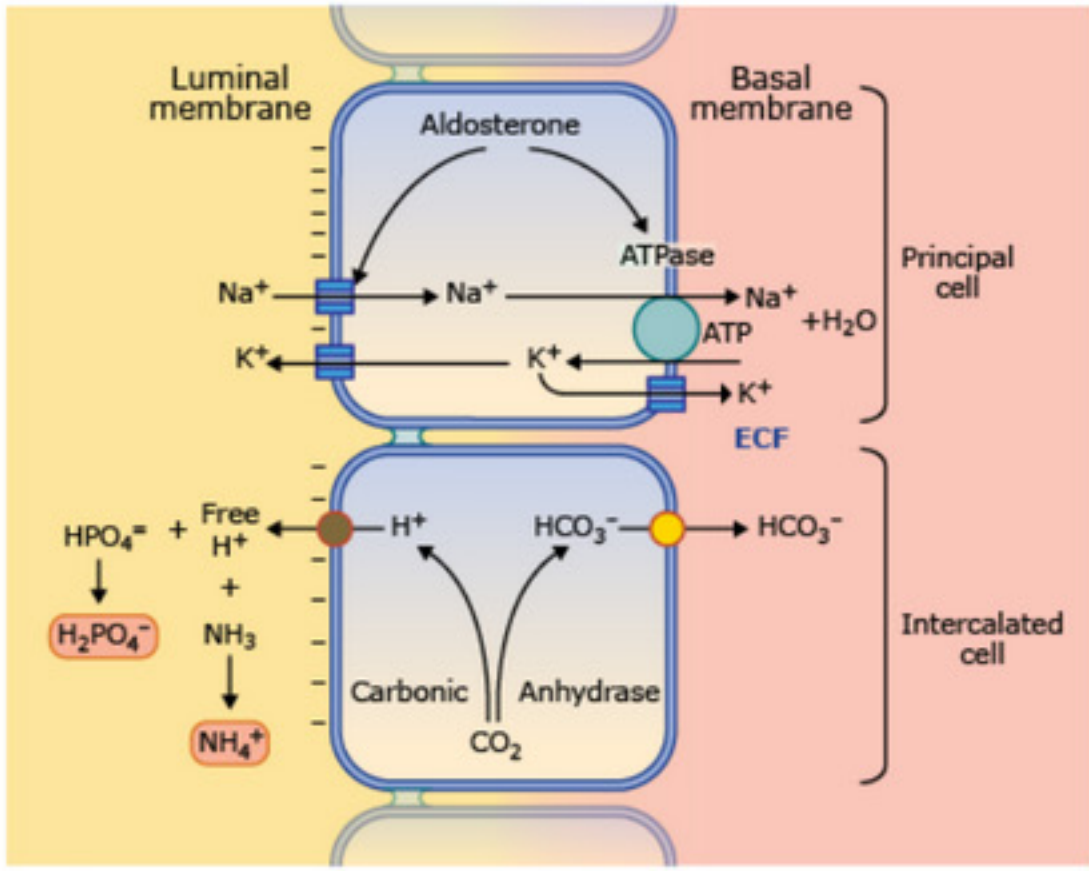
The late distal tubule and the collecting duct are similar. The tubular membrane contains principal and intercalated cells.

4.1 Principal Cells

Principal cells reabsorb sodium and chloride with water and secrete potassium. Unlike the proximal tubule this is a tight system for both sodium and chloride. There is no back diffusion and thus does not exhibit gradient-time dynamics. Sodium diffuses across the luminal membrane through selective sodium channels. It is then actively pumped (Na/K-ATPase) across the basal membrane. Transport at the luminal and basal membrane is controlled by aldosterone. The unique aspect is that an equivalent amount of chloride does not follow the sodium. This creates a negative charge in the luminal fluid. This negative charge promotes potassium and hydrogen secretion into the luminal fluid. Aldosterone control will be discussed in more detail in the endocrine section.

4.2 Intercalated Cells

They are represented by two different populations. Those that secrete hydrogen into the luminal fluid generate brand new bicarbonate which is then secreted into the general circulation. Others do exactly the reverse. They secrete bicarbonate into the luminal fluid and hydrogen into the general circulation. When the body has a net production of fixed inorganic acids the former dominate. In a respiratory alkalosis, for example, the latter dominate forming an alkaline urine.



▲ **Figure 27–4.2** Collecting Duct Transport

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4.3 Diuretics

Potassium sparing diuretics reduce potassium secretion by antagonizing the effects of aldosterone in the late distal and collecting duct. Spironolactone acts by a direct antagonism of the mineralocorticoid receptors. Amiloride acts by an inhibition of sodium flux through channels in the luminal membrane. Both potassium and hydrogen excretion are reduced.

4.4 Hydrogen Secretion and Acidification of the Urine

The body production of hydrogen ions from fixed inorganic acids must be accompanied by an equivalent production of hydrogen ions by the intercalated cells. The hydrogen ions are lost in the urine and the new bicarbonate is secreted into the circulation. Carbon dioxide within the cell first generates equal numbers of hydrogen ions and bicarbonate. The hydrogen ions are then actively secreted into the luminal fluid. Hydrogen ions can be actively pumped until the luminal pH drops to 4.0–4.5. This is the maximum gradient that can be created across the luminal membrane. Almost all the hydrogen ions secreted are buffered. This maximizes hydrogen ion excretion in a small urine volume. Two systems are involved, phosphate buffer system and ammonium.

4.4.1 Phosphate Buffer System

Monohydrogen phosphate is freely filtered and partially reabsorbed in early segments, mainly the proximal tubule. The phosphate delivered to the collecting duct will buffer about one third of the secreted hydrogen ions depending on the diet. The dihydrogen phosphate formed is referred to as titratable acid. Tritratable acid does include some organic buffers. In ketoacidosis, ketone bodies can constitute the main component of titratable acid.

4.4.2 Ammonium

Ammonia is produced by cells of the proximal tubule from glutamine and delivered to the collecing duct. Ammonia production is based on need. In an acidosis, ammonia production increases, in an alkalosis it decreases. Ammonia combines with hydrogen ions to form ammonium. Ammonium is not really a buffer in the urine since titrating the urine back to the pH of blood does not reconvert it to ammonia. Thus, ammonium is often called nontitratable acid. On a diet containing red meat, ammonium is the main form in which acid is lost in the urine.

Phosphate + ammonium = total acid lost in the urine

Total acid lost in the urine = gain of new bicarbonate

4.5 Renal Tubular Acidosis Type I

- Caused by an inability of the collecting duct to secrete fixed acid, and thus an inability to form an acid urine. Urine pH usually greater than six.
- Mechanisms would include impairment of the hydrogen or bicarbonate transport systems and an increased permeability of the luminal membrane allowing the back diffusion of hydrogen from the tubular lumen.
- Characterized by a metabolic acidosis but an inappropriately high urine pH.
- Contrast this with an inability to produce adequate ammonia. The metabolic acidosis would be accompanied with a very low urine pH but a low acid load in the urine (ammonium low).

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5 Renal Failure (Decreased GFR)

5.1 Acute Renal Failure

- Develops fairly rapidly and is generally reversible.
- Azotemia: Increased nitrogenous waste products in the blood, urea and creatinine.
- Prerenal: Decreased blood flow to the kidneys. Continued reabsorption of fluid including urea; creatinine not reabsorbed; BUN:Cr > 15 (15 normal). Increased renin and Angiotensin II.
- Postrenal: Obstruction in urine outflow tract increasing pressure in Bowman's space; azotemia. Initially, small volume with high urine osmolarity, but later increased volume with decreased osmolarity.
- Intrarenal: Acute tubular necrosis. Most affected will be the proximal tubule and thick ascending limb of Henle. These are the most metabolically active cells in the kidney and, thus, most sensitive to ischemia. Necrotic cells block tubule. Recovery takes 1–2 weeks after perfusion is regained due to regenation of tubular cells.

5.2 Chronic Renal Failure

- Develops slowly and is characterized by an irreversible loss of nephrons.
- Remaining nephrons compensate by increasing GFR via increasing glomerular capillary pressure (glomerular hypertension). This accelerates the loss of nephrons and failure.
- Sodium, potassium, and water retention. Can result in hypertension, peripheral edema, and heart failure.
- Hyperphosphatemia and failure to activate vitamin D cause decreased plasma calcium and a secondary hyperparathyroidism.
- Main cause is diabetes; second is hypertension.
- Diabetic nephropathy: often initiated by a glomerular hypertension and elevated GFR. ACE inhibitors (selectively dilates the efferent arteriole) reduce glomerular capillary pressure and GFR.

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Unit 8

Acid–Base Physiology

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1 General Principles

Higher $[H^+] \rightarrow$ lower pH = acidemia (pH < 7.35)
Lower $[H^+] \rightarrow$ higher pH = alkalemia (pH > 7.45)

Basic science textbooks often refer to acidemia as an acidosis. Clinical books refer to acidosis as the process causing the problem.

Plasma $[H^+]$ = 0.00000004 mM/L = 40 nM
Corresponds to a pH of 7.4

The most important acid-base status in a patient is the intracellular environment. This is not easily measured and it is compartmentalized. An estimate is that within the cell the pH is probably close to seven. Measurement of the systemic arterial parameters should be considered an index of the intracellular environment. Under most conditions there is a good correlation between the two compartments. But this is not always the case. In low-output heart failure, reduced perfusion raises capillary CO_2 and decreases plasma pH with corresponding changes within tissues. Under these conditions venous values more accurately reflect the status of the intracellular environment.

1.1 Major Effects of Acidemia

- Impaired cardiac contractility
- Arteriolar dilation, venoconstriction
- Reduced CO, BP, and renal blood flow
- Predisposition to arrhythmias
- Decreased responsiveness to catecholamines
- Hyperventilation
- Decreased strength of respiratory muscles
- Hyperkalemia
- Reduced ATP synthesis
- Inhibition of glycolysis

1.2 Major Effects of Alkalemia

- Arteriolar constriction
- Reduced angina threshold
- Predisposition to arrhythmias
- Hypoventilation
- Hypokalemia
- Reduced plasma ionized calcium, which leads to tetany seizures

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1.3 Buffers

Inorganic strong acids are fully dissociated within the plasma (e.g., HCl, H_2SO_4, H_3PO_4) and never act as buffers. Weak organic acids, depending on the pH, can be partially or completely dissociated. The pH at which the acid is 50% dissociated is referred to as its pKa.

At a lower pH less is dissociated and at higher pH more will be dissociated. At a pH± 1.0 of its pKa the weak acid acts as a good buffer. The pKa of lactic acid is about 3.8; thus, it is almost completely dissociated at a physiological pH and does not act as a buffer. The situation is similar for ketone bodies.

Weak organic acids do not act as buffers under normal physiological conditions. However, when ketone bodies appear in an acid urine, the pH is close to their pKa and they add significant buffering. In fact, in a ketoacidosis, the main titratable acids in the urine can be the ketone bodies.

The CO_2/HCO_3^- system has a pKa of 6.8. It is not a good buffer, but is used to control the $[H^+]$.

At a physiological pH the most important buffers are hemoglobin and other proteins.

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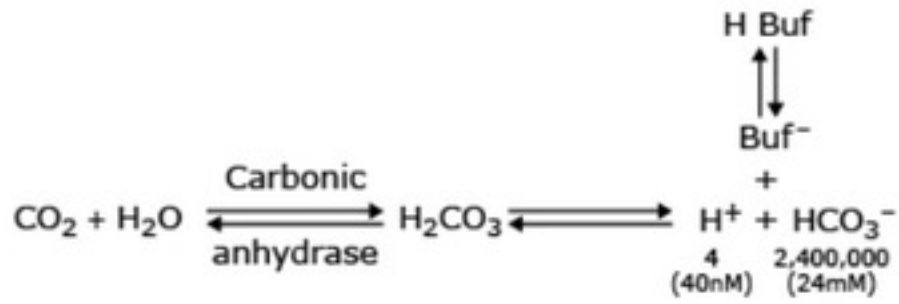
2 Acid–Base Regulation

Acid-base regulation can, in part, be explained using the Henderson-Hasselbach Equation, but, in most disturbances, it is not a useful approach. It has three unknowns. When two are known, the third is fixed. The equation's most useful application is when blood pH and CO_2 are measured it calculates the plasma HCO_3.



Acid-base regulation, disturbances, and compensation can all be explained, at least qualitatively, by the figure at right:

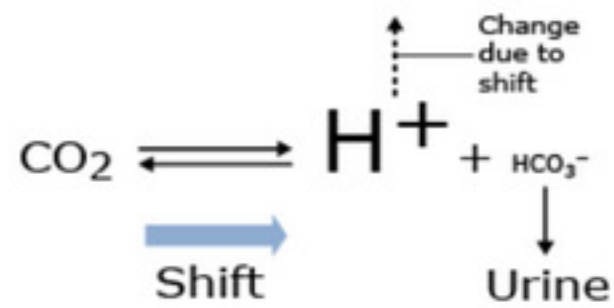
Since only three parameters are monitored clinically the above can be reduced as shown below.

$$CO_2 \rightleftharpoons H^+ + HCO_3^-$$

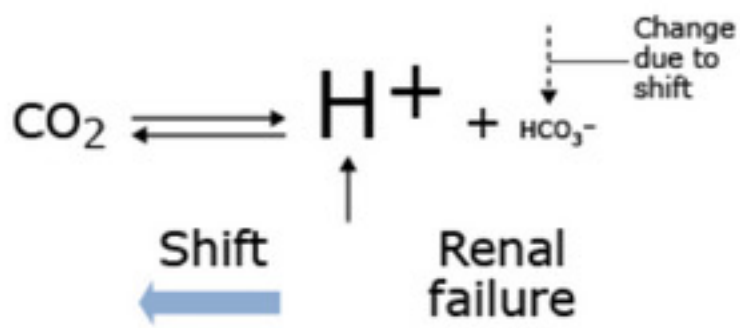
An acid-base disturbance that alters one of the three parameters will shift the reaction left or right to a new equilibrium state.

For example, if acetazolamide decreases HCO_3 reabsorption and there is a net loss of HCO_3 in the urine, this shifts the reaction to the right.

Consequently, HCO_3 decreases (the cause) and the increased H^+ (due to shift) creates a metabolic acidosis.



On the other hand, renal failure causes H^+ to accumulate resulting in a shift to the left consuming HCO_3. The result is the same—increased H^+ (the cause) and a decrease in HCO_3 (due to shift).



In other words, a metabolic acidosis which is characterized by an increase in H^+ and a decrease in HCO_3 can be caused by either a net loss of HCO_3 or an accumulation of H^+. The result is the same.

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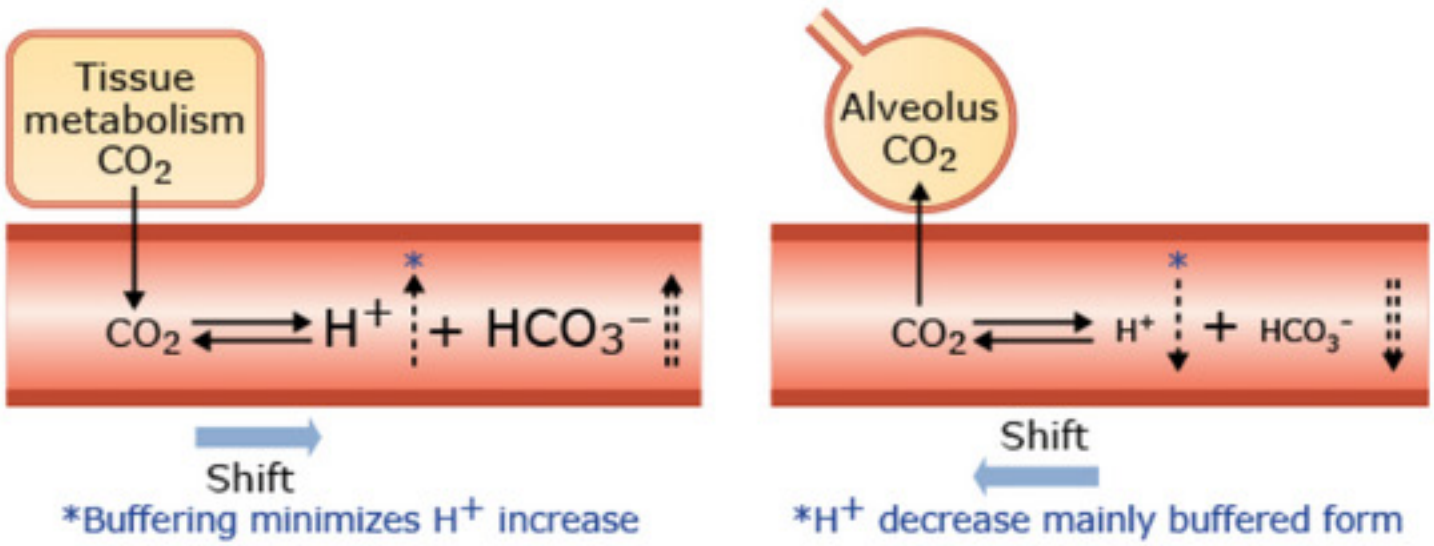
3 Homeostasis and the Steady-State Situation

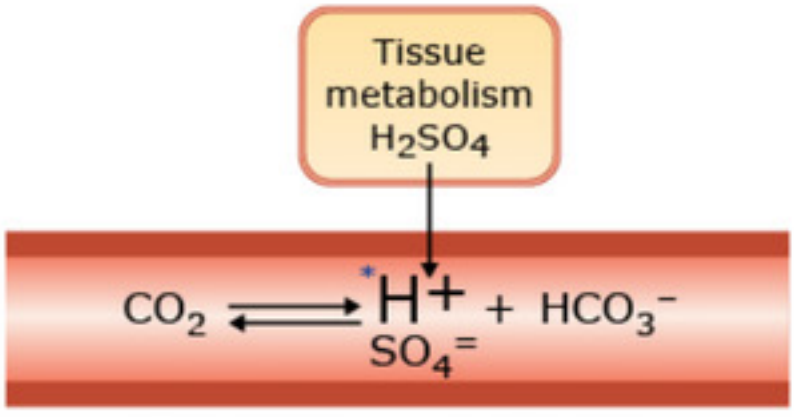
Assuming the individual is on a western diet (including red meat), metabolism is continuously producing acid. CO_2 (volatile acid) and fixed inorganic acids (HCl, H_2SO_4, H_3PO_4, etc.).



▲ **Figure 28–3.0A** Transport and Loss of Tissue CO_2 From the Body

CO_2 is first converted to H^+ and HCO_3. The H^+ is buffered mainly by hemoglobin and the CO_2 is carried to the lung as HCO_3. Here, the reverse occurs and the CO_2 is lost. Vast quantities of CO_2 are lost each day and the only limitation is the transport to the lung and the loss of CO_2 with alveolar ventilation.

With fixed inorganic acids, the situation is more complicated. As shown below, the H^+ and accompanying anions are secreted into the bloodstream. Almost all the H^+ is buffered and transported to the lungs.



*Only slight increase due to buffering

▲ **Figure 28–3.0B** Transport of Fixed Acid in the Blood

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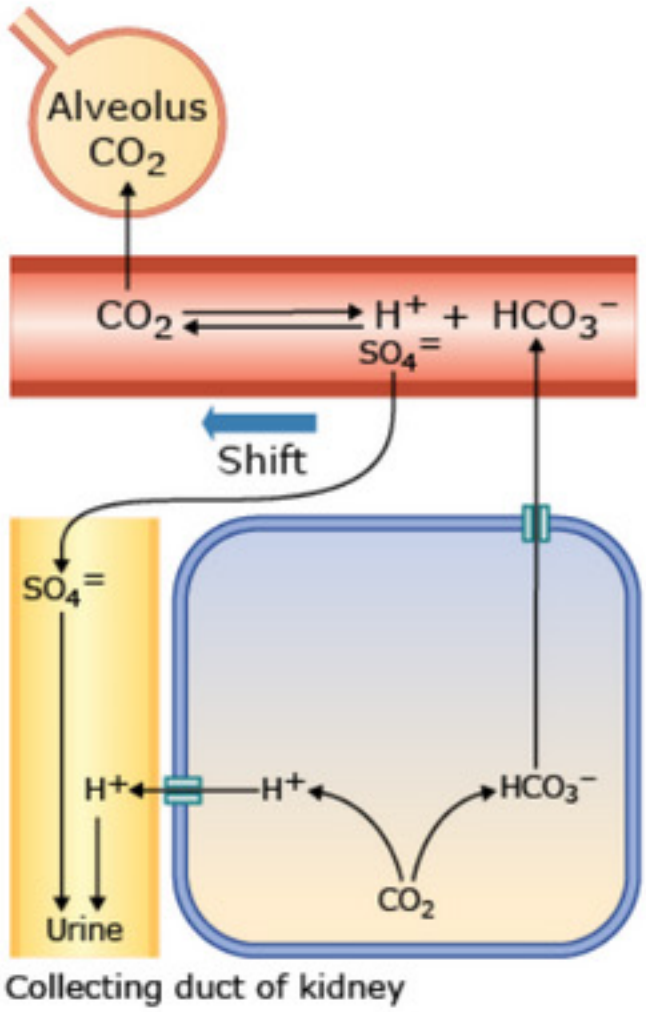
In the pulmonary capillaries, the H^+, mostly released by hemoglobin, shifts the reaction to the left. The H^+ is then lost as CO_2 in the lungs (complete reaction shows H^+ actually remains as part of H_2O). Problematically, when H^+ is lost in the lung there is an equivalent loss of plasma HCO_3. This HCO_3 is replaced by the collecting duct of the kidney.



▲ **Figure 28–3.0C** Fixed Acid Excretion

In steady-state, the loss of HCO_3 in the lung equals the new bicarbonate generated in the collecting duct, which equals the H^+ lost in the urine. In the case of sulphuric acid, the SO_4 negative charges balances the H positive charges lost in the urine.

Organic acids are generally not excreted. They are metabolized to CO_2.

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4 The Primary Disturbances

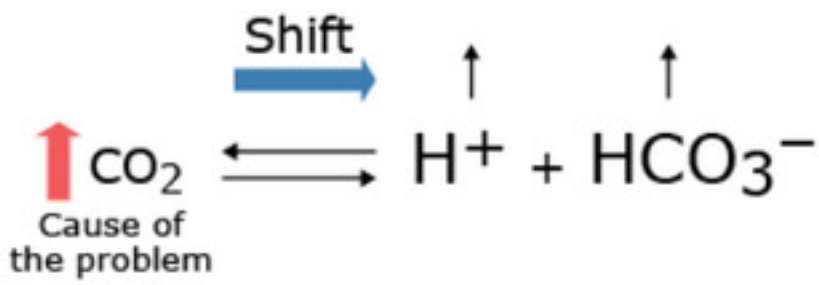
A respiratory problem always originates on the left of the equilibrium with CO_2. This is due to inappropriate alveolar ventilation.

4.1 Respiratory Acidosis

The cause of respiratory acidosis is an increase in the systemic arterial CO_2 due to a state of hypoventilation. This will shift the reaction to the right and the increase in H^+ will create the acidosis.

Note: for every H^+ generated there will be an equivalent increase in HCO_3.

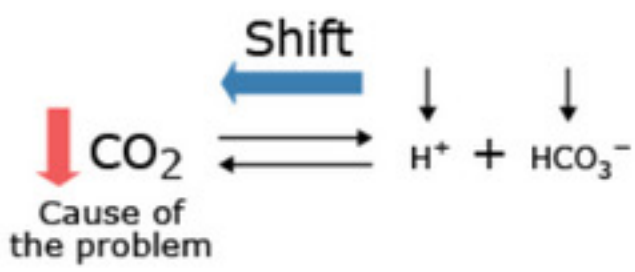
An acute uncompensated respiratory acidosis will be accompanied by an elevated HCO_3^- but it will be a small increase. In general, for every 10 mmHg increase in CO_2, HCO_3 will increase 1 mM.



4.2 Respiratory Alkalosis

The cause of respiratory alkalosis is a decrease in the systemic arterial CO_2 due to hyperventilation. This will shift the reaction to the left. The decrease in H^+ will create the alkalosis.

Note: for every H^+ lost there will be an equivalent decrease in HCO_3. An acute uncompensated respiratory alkalosis will be accompanied by a decrease in HCO_3. Like with acidosis, the change in HCO_3 will be small. For every 10 mmHg decrease in CO_2, the HCO_3 will decrease approximately 2 mM.



In summary, the cause of a respiratory problem is an inappropriate alveolar ventilation and a change in the CO_2. In the acute disorder there will be a small change in HCO_3, but it generally stays in the normal range (uncompensated state).

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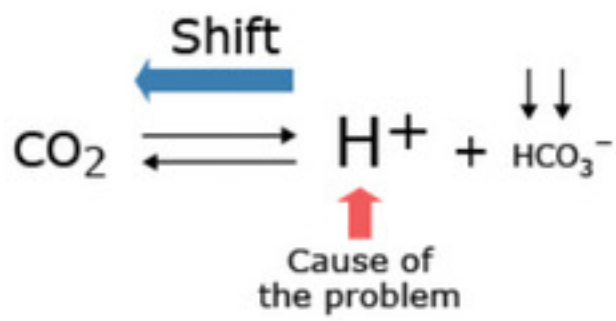
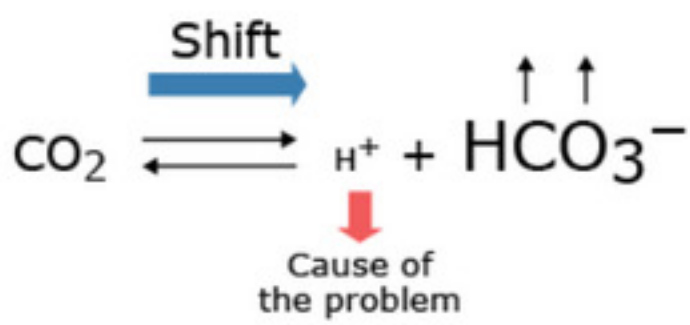
4.3 Metabolic Acidosis

Metabolic acidosis is caused by either a gain in fixed acid (gain in H^+) or a net loss of HCO_3. The loss of HCO_3 can be via the kidney, but it is more frequently caused by diarrhea. The following shows a metabolic acidosis as a gain in fixed acid. The increase in H^+ shifts the equilibrium to the left. In this disorder, there will be a significant decrease in HCO_3. In a metabolic acidosis, HCO_3 will be below the normal range. A shift to the left will generate CO_2; but, we ignore this because the respiratory system will always, if possible, compensate for the metabolic problem. To determine the respiratory response, we assume, if there was none, the CO_2 would remain close to the normal average of 40 mmHg.



4.4 Metabolic Alkalosis

Metabolic alkalosis is caused by a loss of fixed acid (H^+) or a gain in an exogenous load of HCO_3. There is also a contraction alkalosis. This is a loss of HCO_3 free fluid and, thus, a rise in the plasma HCO_3 (it is an anomaly and replacing the fluid eliminates the alkalosis). The most common example of a metabolic alkalosis is the loss of stomach fluids. As shown below, the decrease in H^+ shifts the equilibrium to the right and generating HCO_3. A metabolic alkalosis will be accompanied by an elevated HCO_3.



In summary, a metabolic problem can develop as a primary change in H^+ or a primary change in HCO_3. In both cases, the HCO_3 will be out of the normal range. In an acidosis, it is *below normal* in an alkalosis it is *above normal*.

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5 Determining a Primary Problem

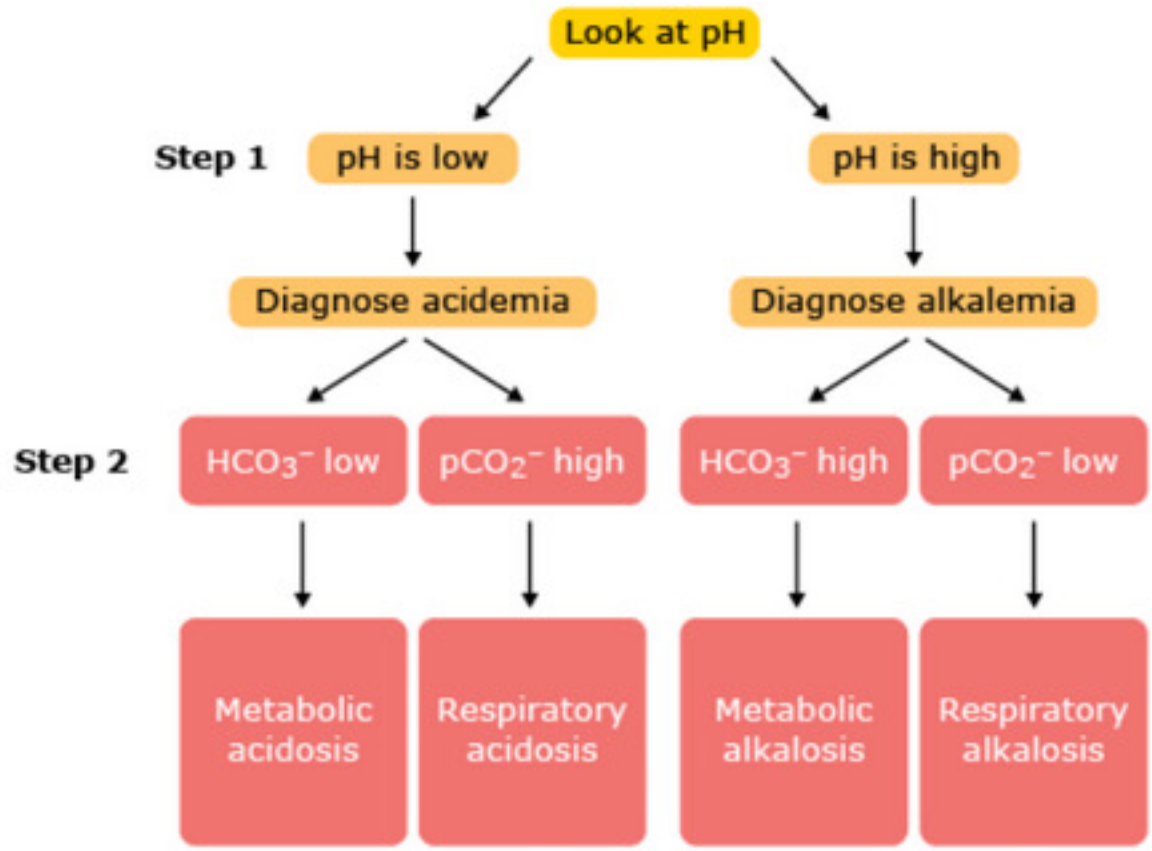
Normal systemic arterial values:

pH	= 7.400 (7.35–7.45)
PCO_2	= 40 mmHg (35–45)
HCO_3	= 24 mM (22–26)

Determining the problem is the first stage in the analysis. It is a two-step approach. Once the problem is established, it is then appropriate to consider compensation.

Step 1: From the pH, is it acidemia (acidosis) or alkalemia (alkalosis)?

Step 2: From the CO_2 and HCO_3, is it respiratory (CO_2), or metabolic (HCO_3), or both?



▲ **Figure 28–5.0** Acid-Base Status From the Analysis of Arterial Blood Gas Data

- Combined respiratory and metabolic acidosis: CO_2 ↑ and HCO_3 ↓
- Combined respiratory and metabolic alkalosis: CO_2 ↓ and HCO_3 ↑

If the CO_2 and the HCO_3 have moved in the opposite direction from normal, it is a *combined* or a *mixed disturbance*. It is more likely to test the combined acidosis than the combined alkalosis.

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Practice Problems: Determine the Disturbance

1. pH = 7.51
PCO_2 = 51
HCO_3 = 40

2. pH = 7.32
PCO_2 = 29
HCO_3 = 15

3. pH = 7.32
PCO_2 = 50
HCO_3 = 25

4. pH = 7.51
PCO_2 = 30
HCO_3 = 23

5. pH = 7.24
PCO_2 = 48
HCO_3 = 20

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6 Compensation

- In a respiratory problem *the kidneys compensate*
- In a metabolic problem *the respiratory system compensates*

Compensation is seldom complete (i.e., the arterial pH returns toward, but not back to, the normal range). The kidneys will also respond in a metabolic disturbance by returning HCO_3 toward normal. This is more correctly considered, not compensation, but an attempt to eliminate the disturbance.

6.1 Respiratory Compensation

In a metabolic disturbance there should be a partial respiratory compensation. The respiratory system responds quickly to a metabolic problem.

- Metabolic Acidosis: hyperventilation ↓ PCO_2
- Metabolic Alkalosis: hypoventilation ↑ PCO_2

The expected change of CO_2 can be calculated as shown in the table below. If the CO_2 goes beyond the expected change, then it is a combined metabolic-respiratory problem.

▼Table 28–6.1

Condition	Primary Change	Expected Compensation
Metabolic Acidosis	Decrease in HCO_3	Expected $\Delta pCO_2 = 1.3 \times \Delta HCO_3^-$ For every drop of 1 mEq/L in HCO_3^-, the pCO_2 decreases by 1.3 ("blowing off" CO_2)
Metabolic Alkalosis	Increased HCO_3^-	Expected $\Delta pCO_2 = 0.7 \times \Delta HCO_3^-$ For every increase of 1 mEq/L in HCO_3^-, the pCO_2 increases by 0.7 ("retaining" CO_2)

6.2 Renal Compensation

Unlike the respiratory system, the kidney is slow to respond to a disturbance. Thus, acute respiratory disturbances will be uncompensated. In an acidosis, the kidney increases the production of HCO_3 and the excretion of acid in the urine. Plasma bicarbonate rises. In an alkalosis the kidney excretes HCO_3 (alkaline urine). Plasma bicarbonate decreases.

- Partially compensated respiratory acidosis: HCO_3 above the normal range.
- Partially compensated respiratory alkalosis: HCO_3 below the normal range.

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▼ **Table 28–6.2**

Respiratory		
Condition	**For every PCO_2 increase of 10 mmHg, HCO_3 changes by**	
Acute		
Acidosis	↑	1 mEq/L
Alkolosis	↓	2 mEq/L
Chronic		
Acidosis	↑	4 mEq/L
Alkalosis	↓	5 mEq/L

The expected compensatory changes in CO_2 and HCO_3 are not likely to be tested on Step 1.

Practice Problems: Determine Any Compensatory Changes

1. pH = 7.51 partially compensated metabolic alkalosis

PCO_2 = 51

HCO_3 = 40

The kidneys, if functioning, would excrete HCO_3 (alkaline urine). This returns the person to normal and eliminates the metabolic alkalosis. As the individual returns toward normal ventilation also returns toward normal (ventilation increases). It is difficult to maintain an alkalosis if the kidneys respond appropriately. A maintenance phase of a metabolic alkalosis often indicates the kidneys are not responding by eliminating HCO_3. For example, with severe vomiting the alkalosis is accompanied with a volume contraction.

To maintain electrical neutrality Na^+ must accompany the HCO_3^- in the urine. Because volume regulation may take priority over acid-base regulation, homeostatic mechanisms will conserve sodium preventing the urinary loss of HCO_3^-.

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2. pH = 7.32 partially compensated metabolic acidosis
PCO_2 = 29
HCO_3 = 15

The renal response to the acidosis should be to increase the total acid lost in the urine. Ammonia production in the proximal tubule would increase. The increased acid lost in the urine would be reflected by elevated urine ammonium not simply by a low urine pH. Ammonium is not a standard clinical measurement. Instead, it is indirectly estimated by measuring the urine anion gap.

Urine: + charges = − charges
Positive charges are approximated as: $Na^+ + K^+ + NH_4^+$
Negative charges are approximated as: Cl^-

Low ammonium in the urine: $Na^+ + K^+ - Cl^- \approx 0$
High ammonium in the urine: $Na^+ + K^+ - Cl^- = (-)$

The calculated negative urine anion gap is due to unmeasured positive ions in the urine, mainly NH_4^+.

The increase acid lost in the urine would be reflected by an increase in HCO_3 production by the kidney. A rise in plasma HCO_3 indicates a return toward normal. If the acid production exceeds the production of new HCO_3 by the kidney, plasma HCO_3 may continue to decline.

3. pH = 7.32 uncompensated or acute respiratory acidosis
PCO_2 = 50
HCO_3 = 25

4. pH = 7.38 kidney compensation of the respiratory acidosis
PCO_2 = 50 (elevated plasma HCO_3)
HCO_3 = 28

5. pH = 7.51 uncompensated or acute respiratory alkalosis
PCO_2 = 30
HCO_3 = 23

6. pH = 7.48 kidney compensation of the respiratory alkalosis
PCO_2 = 31 (decreased plasma HCO_3)
HCO_3 = 20

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7 Plasma Anion Gap

- In the plasma the cations balance the anions.
- However, many plasma cations and anions are not routinely measured.
- Primary measured ones: Na^+, Cl^-, HCO_3^-.

The real balance is given by the equation:

$$[Na] + [\text{other cations}] = [Cl] + [HCO_3] + [\text{other anions}]$$

Which rearranges to:

$$[Na] - ([Cl] + [HCO_3]) = \underbrace{[\text{other anions}]}_{\text{significant}} - \underbrace{[\text{other cations}]}_{\text{not significant}}$$

$$= \text{anion gap}$$

Normal anion gap = 3 – 12

An anion gap > 12 could indicate a metabolic acidosis

An anion gap > 20 always indicates a metabolic acidosis

Non anion gap metabolic acidosis (hyperchloremic metabolic acidosis):

- Diarrhea
- Type I renal tubular acidosis
- Type II renal tubular acidosis

In all three of the above, the anion associated with the acidosis is lost in the urine accompanied by sodium.

Anion gap metabolic acidosis (anions retained):

- Lactic acidosis
- Ketosis
- Renal failure
- Methanol
- Ethylene glycol
- Salicylates

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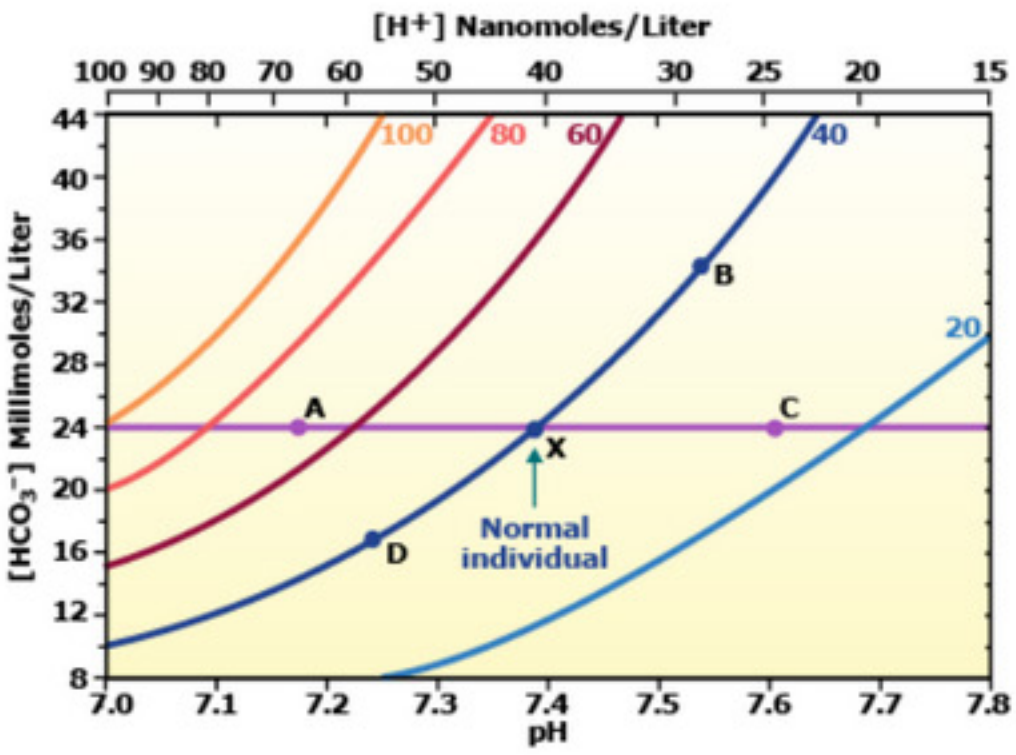
8 Davenport Diagram

Horace Davenport developed a graphical display for the acid-base disorders and their compensations. Arterial pH is on the X-axis and HCO_3 is on the Y-axis. As stated earlier the Henderson-Hasselbalch equation has three variables, pH, HCO_3, and PCO_2. If two are known, the third is fixed. Therefore, at a given pH and HCO_3 there can only be one value for CO_2. CO_2 isobars can be constructed and appears as curved lines on the graph. The CO_2 isobar of 40 must go through the normal point where pH = 7.4 and HCO_3 = 24. In the theoretical cases where there is a metabolic disturbance, but no respiratory compensation, CO_2 remains at 40 mmHg. Thus, the CO_2 isobar of 40 mmHg represents metabolic disturbances with no respiratory compensation. In addition, a straight line with a slight slope is also included. This is a *CO_2 titration curve* and represents uncompensated (acute) respiratory disturbances. The intersection of the CO_2 40 mmHg isobar and the CO_2 titration curve (forming an *X*) represents a normal individual. Each leg of the X represents a simple disturbance with no compensation.



A = acute or uncompensated respiratory acidosis (acute hypoventilation)

B = uncompensated metabolic alkalosis

C = acute or uncompensated respiratory alkalosis (acute hyperventilation). An individual who just arrived at a high altitude airport.

D = uncompensated metabolic acidosis

▲ **Figure 28–8.0A** Davenport Diagram With Primary Disturbances and No Compensation

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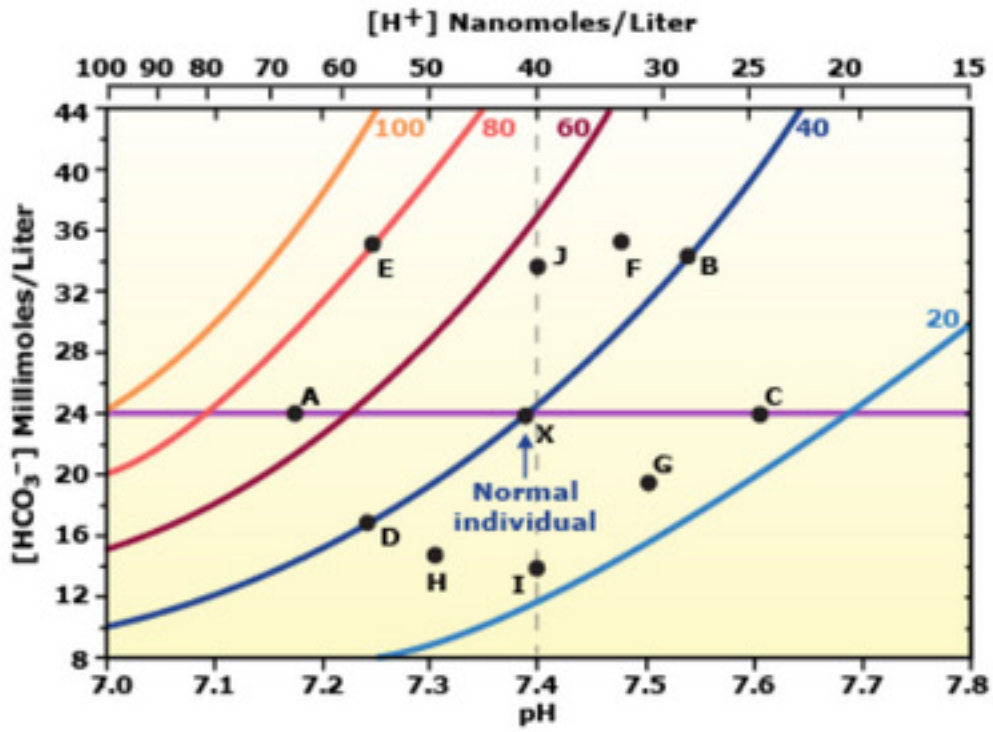
In the following figure, the dashed line at any point other than the normal point represents a fully compensated disorder (pH = 7.4). Points between an uncompensated disturbance line, legs of the X, and the dashed line represent a partially compensated state.



E = partially compensated respiratory acidosis

F = partially compensated metabolic alkalosis

G = partially compensated respiratory alkalosis

H = partially compensated metabolic acidosis

I = fully compensated metabolic acidosis or fully compensated respiratory alkalosis (adaptation to high altitude)—could also be a combined respiratory alkalosis and metabolic acidosis

J = fully compensated respiratory acidosis or fully compensated metabolic alkalosis. Could also be a combined respiratory acidosis and a metabolic alkalosis

▲ **Figure 28–8.0B** Davenport Diagram With Disturbances and Compensation

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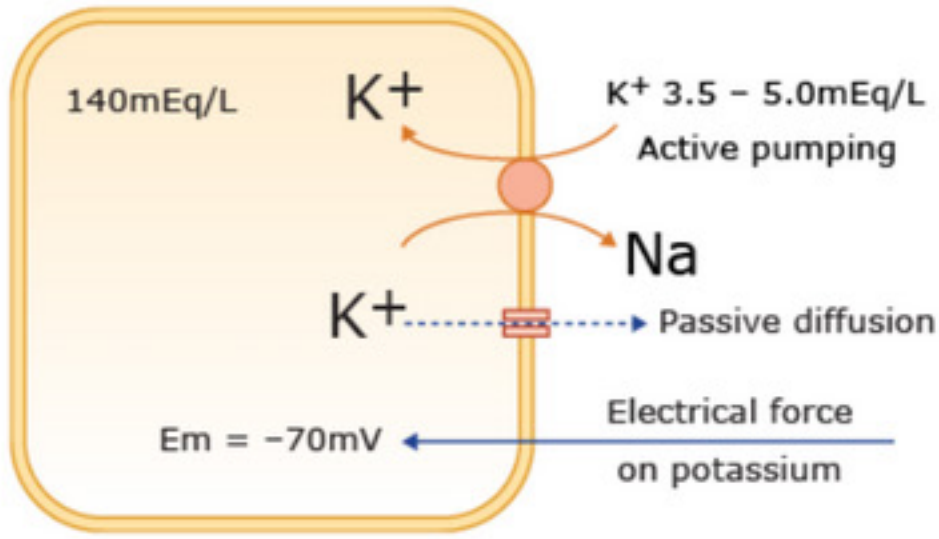
9 Pathophysiology of Potassium Dynamics

9.1 Potassium Regulation

- Concentration in ECF closely regulated; < 3.5 mEq/L = hypokalemia, > 5 mEq/L = hyperkalemia.
- Acute regulation; insulin, catecholamines.
- Chronic regulation; aldosterone.
- Almost all body potassium is in the ICF (95–98%), 2–3% ECF.
- Inward pumping of potassium and negative membrane potential that maintains the high ICF.



▲ **Figure 28–9.0** Normal Potassium Dynamics in the Steady-State

9.2 Pathophysiology

9.2.1 Causes of Hypokalemia

- Diuretic use is the most common cause.
- Hyperaldosteronism: Renal function intact (e.g., Conn syndrome), renal arterial stenosis, renin secreting tumor.
- ECF → ICF; metabolic alkalosis, hypoosmolar state.
- ↑ Insulin, catecholamines.
- Diuresis with ketoacidosis, renal tubular acidosis.

9.2.2 Consequences of Hypokalemia

- More negative resting membrane potential; decreased excitability in nerves and muscle.
- Skeletal muscle weakness, arrhythmias.
- EKG: heightened U waves, depressed T waves.

9.2.3 Causes of Hyperkalemia

- Hypoaldosteronism (pharm; ACE inhibitors, potassium-sparing diuretics).
- Renal failure (usually with hyperaldosteronism).
- Hypoinsulinemia, ↓ catecholamine responses (β-blockers).
- Muscle trauma, tissue necrosis (burns).
- ICF → ECF; metabolic acidosis, hyperosmolar states.

9.2.4 Consequences of Hyperkalemia

- Arrhythmias most serious consequences.
- Neuromuscular weakness.
- EKG; elevated T waves.

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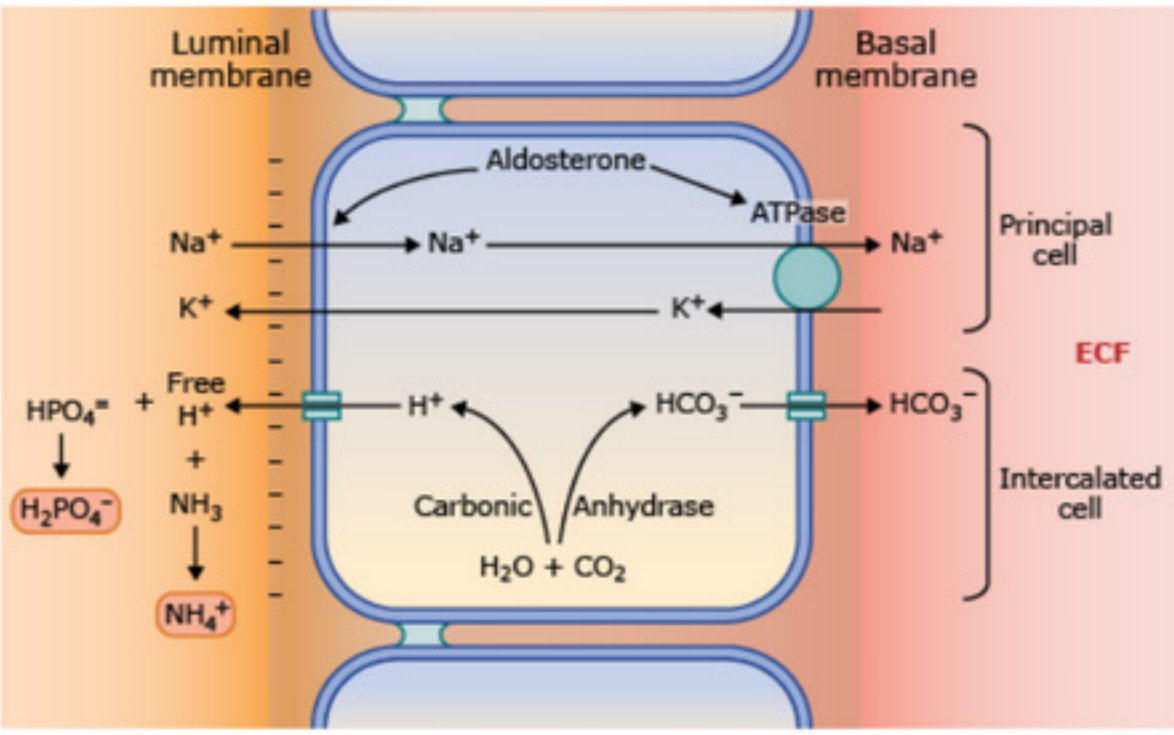
10 Renal Response to Acid–Base Disorders



▲ **Figure 28–10.0** Ion Dynamics in the Renal Collecting Duct

10.1 Metabolic Acidosis

Increased secretion of H^+ in the collecting ducts decreases the negative charge in the lumen which reduces potassium secretion. This can aggravate the hyperkalemia of a metabolic acidosis. However, if there is a diuresis with a natriuresis the increase flow to the collecting duct increases the excretion of potassium.

10.2 Metabolic Alkolosis

Decreased secretion of H^+ in the collecting ducts increases the negative charge in the lumen which can increase potassium secretion. This can aggravate the hypokalemia of a metabolic alkalosis.

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Unit 9

Gastrointestinal Physiology

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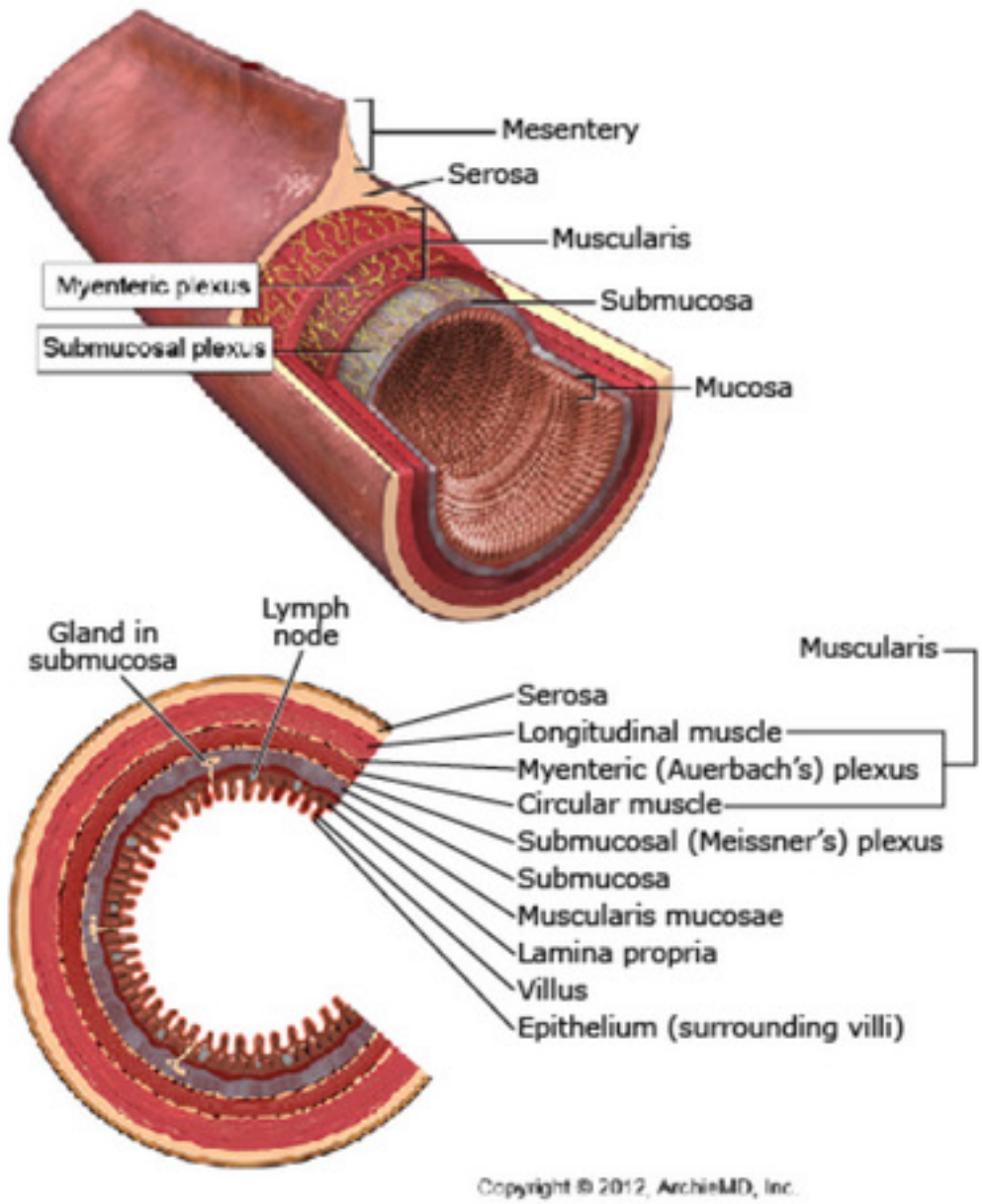
1 Structure of the GI Tract

The wall of the GI tract consists of specialized layers.



▲ **Figure 29–1.0** Structure of the GI Tract

1.1 Mucosa (Three Layers)

- **Epithelium:** The single innermost layer of cells; some cells are absorptive, others are secretory, and a few have an endocrine function. Often organized into villi and crypts. Villi are finger-like projections and crypts are invaginations in the epithelium.
- **Lamina Propria:** Contains small blood vessels, nerves, and lymphatic vessels.
- **Muscularis Mucosa:** The layer of smooth muscle that acts to contract the mucosa into folds.

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1.2 Submucosa

A layer of thick connective tissue that is responsible for much of the distensibility of the GI tract. The outer surface has the submucosal plexus, a nerve net mainly involved in secretory activity, and along with the myenteric plexus, they form the enteric nervous system. This system has input from the sympathetic and parasympathetic systems, but can relay reflexes independent of the central nervous system.

Muscularis Externa: Consists of an inner circular and outer longitudinal layer. The coordinated contractions of these layers mix and propel the chyme along the tract. The myenteric plexus between the muscle layers coordinates the muscle activity.

Serosa: The outermost layer consists of connective tissue and a surface layer of epithelial cells. It is part of the mesentery that suspends organs. In addition, it secretes a thin, watery fluid that lubricates abdominal organs to provide friction-free movement.

1.3 Nervous Control

There is an integration of the autonomic and enteric nervous systems to provide overall control of GI processes. The input of the sympathetics and parasympathetics tend to have, as expected, opposite effects.

1.3.1 Parasympathetics

The vagus nerve innervates structures from the esophagus to the proximal colon. The pelvic nerves innervate the distal colon. Preganglionic neurons terminate within the end-organ and release acetylcholine acting on nicotinic receptors. Overall, parasympathetics increase motility and secretions. In addition to acetylcholine, vasoactive intestinal peptide and gastrin-releasing peptide act as transmitters.

1.3.2 Sympathetics

Postganglionic neurons innervate blood vessels and cause constriction. Other sympathetics innervate glandular structures and there are synapses with the enteric nervous system. Unlike parasympathetics, which increase activity, sympathetic activity inhibits smooth muscle activity and slows processes overall. An exception to this is the smooth muscle of sphincters, which contract in response to the sympathetics.

This unit provides an integrative presentation of the processes involved as food material and chyme pass from the mouth to the terminal colon. The smooth muscle activity is complex and the cells have the characteristics as presented in the muscle unit:

- Cells form an electrical syncytium via gap junctions.
- Stretch produces a contractile response via action potentials.
- Low ATPase activity and contractions that do not result in fatigue, unless the tissue becomes ischemic.
- Action potentials mainly due to the entry of Ca^{++} through slow channels.

The GI tract has regional pacemaker activity. Originally thought to reside within smooth muscle cells, it is now thought to originate with interstitial cells. Because of this pacemaker activity, there is always some residual motor activity in the GI tract.

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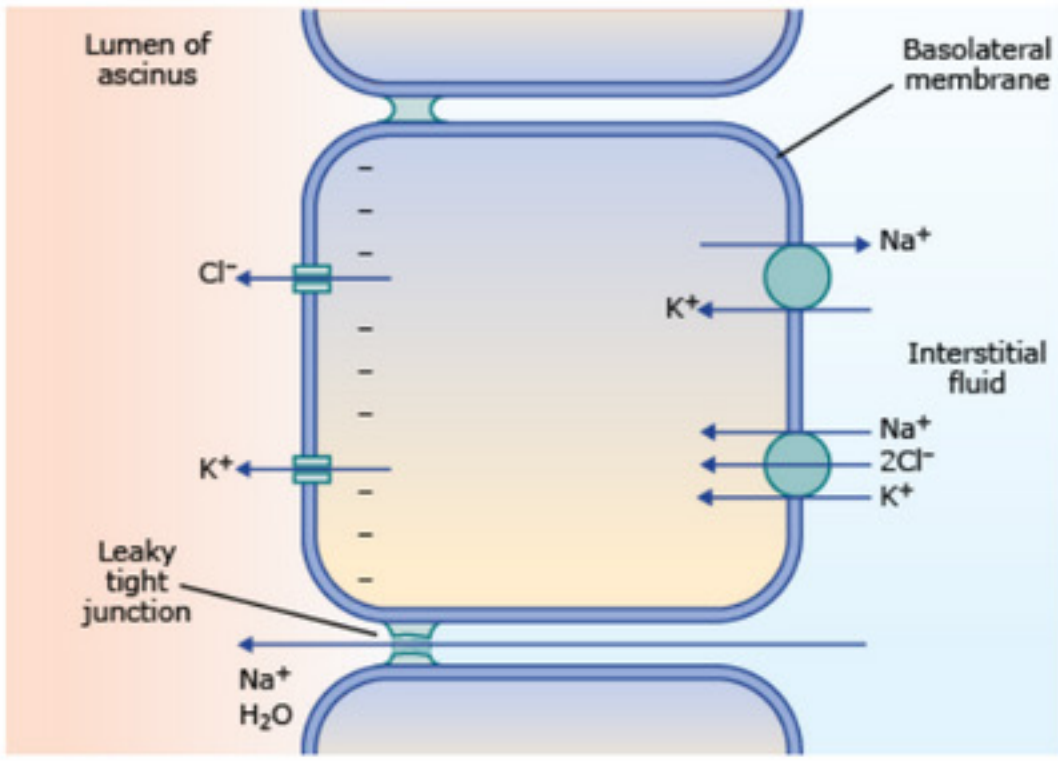
2 The Mouth and Salivary Secretion

- The main function of the mouth is pulverizing the food, lubricating, and moistening it with salivary secretions. There is also some minor enzymatic digestion of complex carbohydrates.
- Salivary secretions are of two types: Serous, which is a low-viscosity *watery* fluid, and a highly viscous fluid containing mucin.
- Parotid glands secrete the serous-type fluid; the submandibular and sublingual secrete a mixture, but the fluid contains a significant amount of mucin.
- Control of salivary secretion is entirely nervous, with parasympathetic stimulation the dominant effect. Sympathetics will also increase secretions, but at a lower rate and the fluid will have a much higher viscosity.

2.1 Salivary Secretions

- Salivary secretion is a two-stage process: Fluid is initially formed in the acinus and then modified by the salivary duct.
- In the acinus, the initially formed fluid is isotonic and the electrolyte composition is the same as the interstitial fluid.
- Although powered by the Na^+/K^+-ATPase pump, the acinar fluid is said to result from a *chloride pump*, as shown in the following figure.
- On the basolateral membrane, Cl^- and K^+ are taken up by secondary transport. Cl^- is moved against a concentration and against an electrical gradient.
- The chloride then diffuses passively through channels in the luminal membrane. The passive movement of Cl^- pulls water and other electrolytes (chloride pump) to form the isotonic fluid.
- As the fluid moves through the salivary ducts, NaCl is reabsorbed but, because the duct membrane has a low permeability to water, duct fluid becomes hypotonic. This is the only hypotonic fluid secreted by the GI tract. At the same time, NaCl is reabsorbed K^+ and HCO_3^- are secreted.



▲ **Figure 29–2.1A** Transport Processes Forming Salivary Ascinar Fluid

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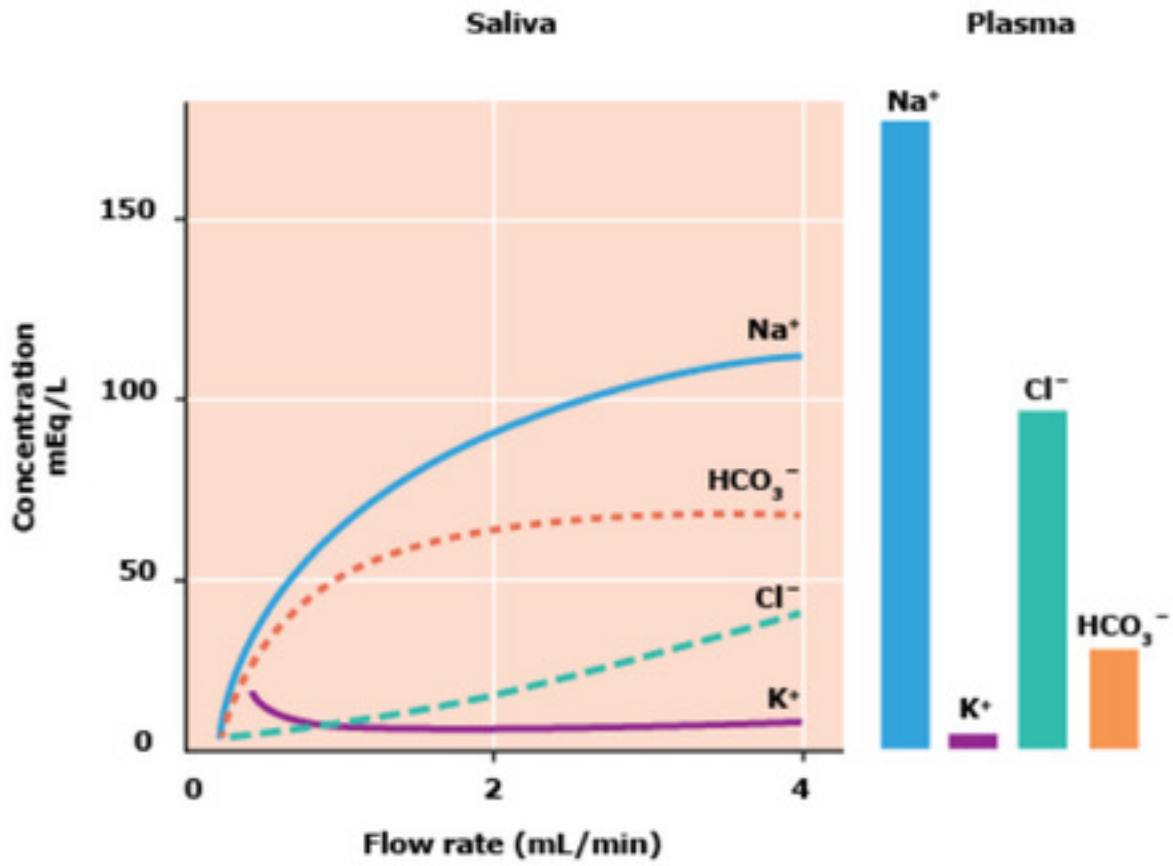
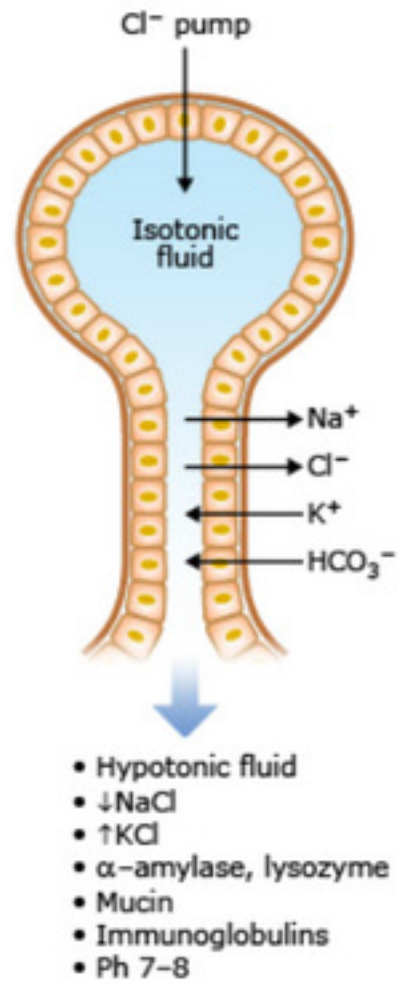
- Salivary secretions contain organic material, including α-amylase, that begins the digestion of carbohydrate. Salivary α-amylase is not a required enzyme for digestion.
- Electrolyte composition and the effect of flow are shown in the following figure.



▲ **Figure 29–2.1C** Salivary Ion Concentrations Versus Flow Rate



▲ **Figure 29–2.1B** Salivary Duct Transport

2.2 Swallowing

- Can be initiated voluntarily but, once initiated, it is a reflex via the medulla that follows a rigid sequence of events from the pharynx to the proximal stomach.
- There are afferent pharyngeal touch receptors and efferent motor effects via the 5th, 9th, 10th, and 12th cranial nerves that initiate the timed events in swallowing.
- In the pharyngeal stage of swallowing, the food passes through the pharynx into the esophagus. There is an inhibition of ventilation and blockage of the larynx to prevent food from entering the trachea.
- The esophageal stage consists of four separate events:
  1. **Relaxation of the Upper Esophageal Sphincter (UES):** The upper one third of the esophagus is skeletal muscle and the UES is a thickening of striated muscle. As such, it requires neural activity to remain constricted. Thus, opening the sphincter involves a decrease in neural activity.
  2. **A Primary Peristaltic Wave:** This is a continuation of the peristaltic wave initiated in the pharynx and is part of the swallowing reflex. Distention of the esophagus will initiate secondary peristaltic waves that, in many cases, are required to complete the movement of the food bolus into the stomach.

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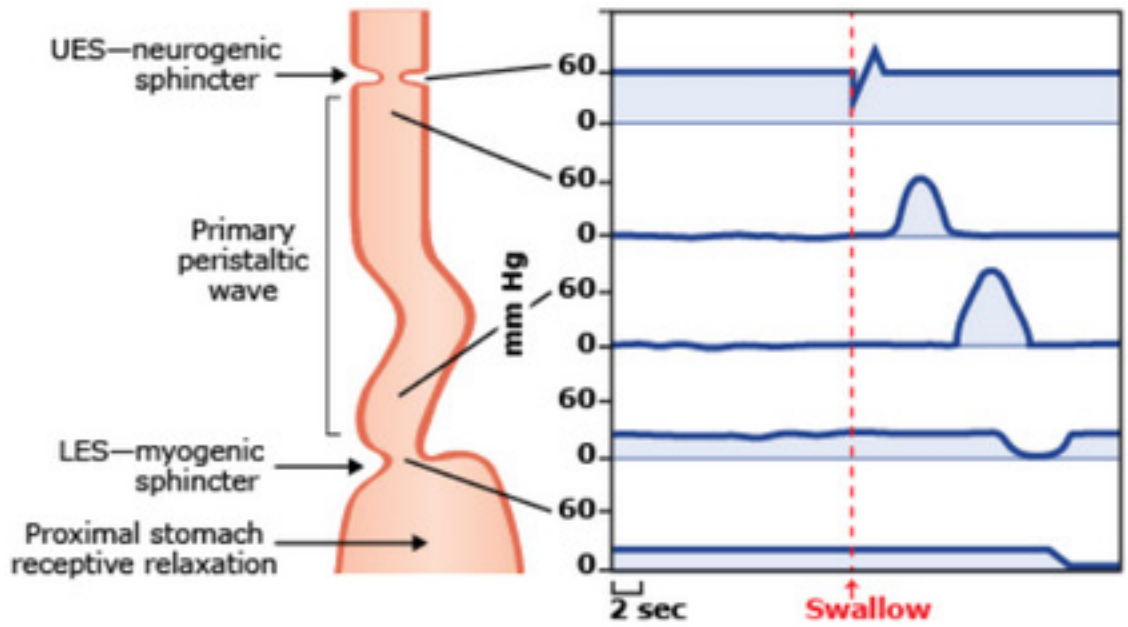
3. **Relaxation of the Lower Esophageal Sphincter (LES):** The lower two thirds of the esophagus is smooth muscle, and a circular band forms the LES, which exhibits an intrinsic contraction without neural input. Relaxation results from the release of a vagal inhibitory transmitter, which is mainly VIP (vasoactive intestinal peptide).
4. **Receptive Relaxation:** Relaxation of the proximal stomach, which prevents an increase in stomach pressure flowing entry of the food bolus.



▲ **Figure 29–2.2** The Sequential Events of Swallowing

2.3 Pathophysiology

- Paralysis of the muscles of swallowing, as it occurs in myasthenia gravis or muscle dystrophy, can disrupt normal swallowing.
- Anesthetics inhibit the swallowing reflux, and vomiting with aspirations into the trachea can cause asphyxia.
- Achalasia is a neurological failure within the myenteric plexus preventing relaxation of the LES. It can be coupled with a loss of peristalsis. The bolus can then remain in the esophagus, causing a local distension.

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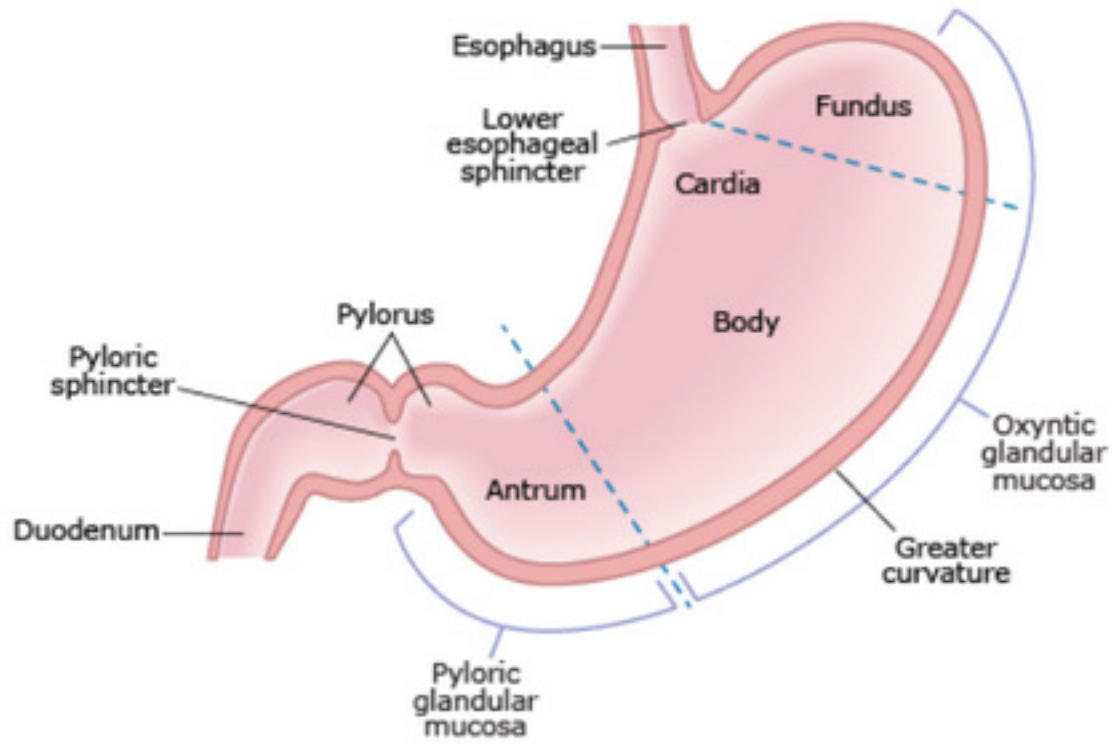
3 The Stomach



▲ **Figure 29–3.0** Functional Divisions of the Stomach

3.1 Motor Functions

- The stomach can be divided into various regions, but, overall, the upper stomach has a storage function, has a lesser amount of smooth muscle, and exhibits receptive relaxation. The lower region (antrum) has the greater amount of muscle and produces the strong, peristaltic contractions.
- On the greater curvature, interstitial cells act as pacemakers and create the basic electrical rhythm.
- As food enters the stomach, due to stretch, vasovagal reflexes reduce muscle tone in the upper stomach but increase the intensity of the peristaltic contractions in the lower stomach.
- Peristaltic constrictor waves, considered mixing waves, begin in the mid-stomach and proceed toward the antrum. The pyloric valve is tightly constricted so little passes into the duodenum.
- As the peristaltic waves become more intense, and receptive relaxation diminishes, pressure increases and a small amount of liquefied chyme is pumped into the duodenum.
- Stomach emptying is mainly controlled from the duodenum. Reflexes and hormonal inhibition slow or stop stomach emptying in response to duodenal distension, acidity, and high osmolarity of the chime. This allows sufficient time for digestion and absorption in the small intestine.

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3.2 Hormonal Control of the GI Tract

- Gastrin is released from *G cells* mainly in the stomach antrum in response to parasympathetic stimulation, peptides, and stomach distension. Gastrin's main effect is stimulating stomach secretions but it also increases constriction of the LES, which protects against GERD. Gastrin also causes a generalized increase in stomach motility. As such, it can be considered to promote stomach emptying. Stomach acid inhibits the secretion of gastrin. A non-acid-producing stomach is associated with elevated circulating gastrin.
- Cholecystokinin (CCK) is released from the duodenum *"I" cells* in response to polypeptides and fatty acids. It causes contraction of the gallbladder and relaxation of the sphincter of Oddi to allow bile to flow into the duodenum, but it also inhibits stomach motility. CCK stimulates enzymatic secretions of the pancreas. This is an extremely important action, as the pancreatic enzymes are required for the digestion of carbohydrate, protein, and fat.
- Secretin released from the duodenal *"S" cells* in response to stomach acid entering the duodenum causes increased fluid flow from the pancreas carrying HCO_3^- into the duodenum to neutralize that acid. Secretin also decreases motility and acid secretion in the stomach.
- GIP (gastric inhibitory peptide, or glucose-dependent insulinotropic peptide) released from the duodenum in response to carbohydrate and fat. It weakly decreases stomach motility. It also stimulates insulin release in response to glucose. Because of this effect, oral glucose gives a greater insulin response than IV glucose.

3.3 Gastric Secretions

Gastric secretions are from surface, mucus-secreting epithelial cells and two types of tubular glands—the oxyntic (gastric) glands and the pyloric glands.

3.3.1 Surface Epithelial Cells

- These cells line the surface of the stomach and secrete a highly viscous alkaline (HCO_3^-) gel, which coats the entire stomach lining.
- Protect the stomach lining from the caustic actions of HCl. Even though stomach contents can have a pH as low as 2.0, the surface of the epithelial cells is maintained close to 7.
- The acid slowly wears away the protective gel, so a continuous secretion is required.
- Parasympathetic stimulation, surface contact with food, or an irritation directly stimulates secretion.
- Secretions also lubricate the food and assist with transport.

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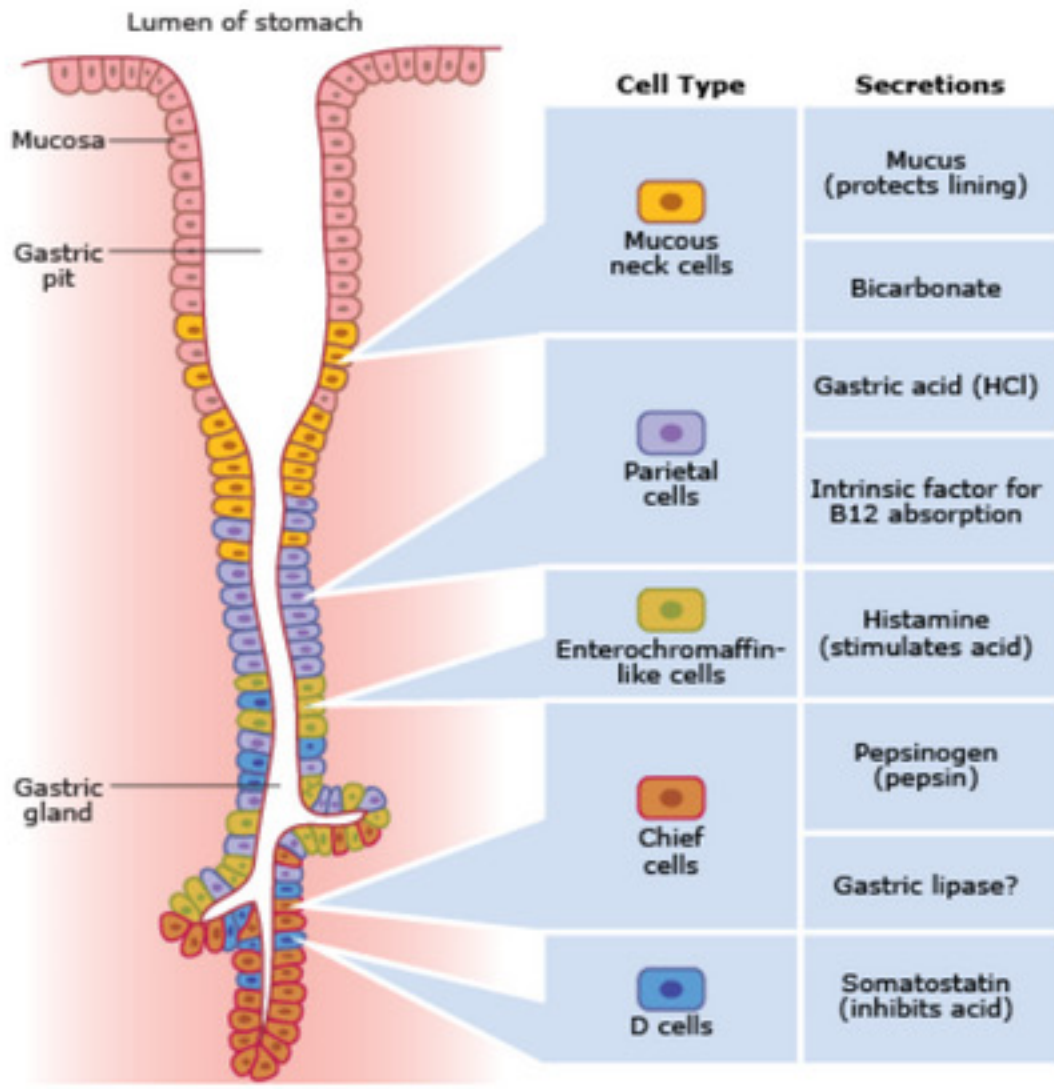
3.3.2 Gastric Glands

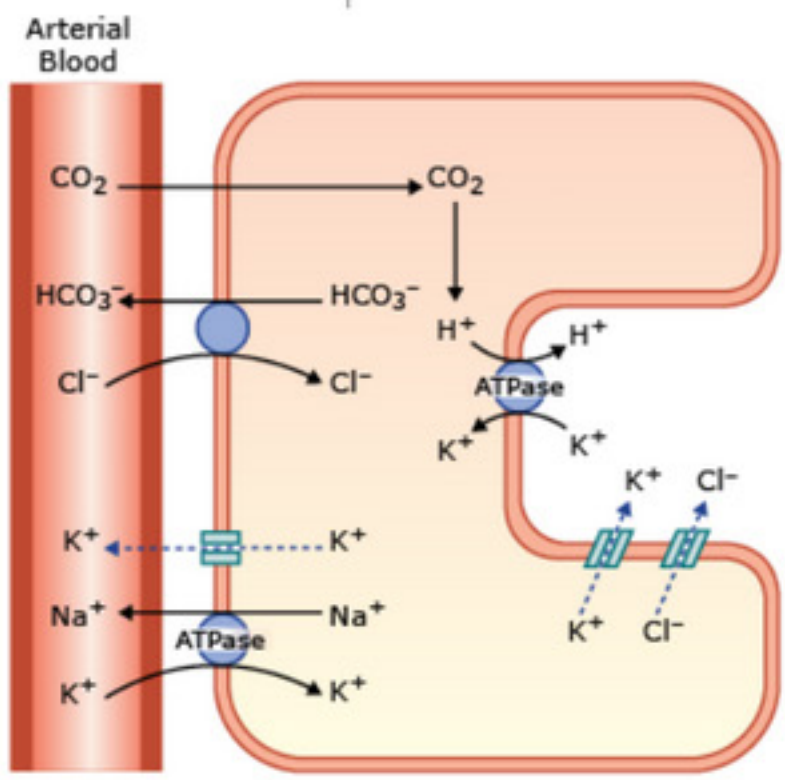


▲ **Figure 29–3.3A** Structure of the Gastric Glands

Located in the upper and middle regions of the stomach and contain three secretory cells.

1. Parietal Cells:

- These cells secrete HCl and intrinsic factor. Intrinsic factor is required for the intestinal absorption of vitamin B12 and is the only secretory product of the stomach that is required for life.
- Parietal cells operate in close association with the enterochromaffin-like cells (ECL cells), which secrete histamine. Histamine acts as a paracrine and stimulates the H_2 receptors on the parietal cell. Gastrin → ECL cell → histamine → parietal cell → HCl.
- Parietal cells are directly stimulated by acetylcholine, histamine, and gastrin.
- The demand for CO_2 by the parietal cells following a meal is so great that they extract CO_2 from the capillary blood.
- Carbonic anhydrase catalyzes the conversion to H^+ and HCO_3^-.



▲ **Figure 29–3.3B** Parietal Cell Secretion

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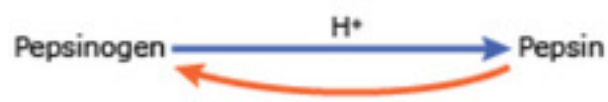
- The H^+ is pumped into the lumen by a H^+/K^+- ATPase.
- The higher the secretion rate, the higher the H^+ concentration down to a pH of about 0.8.
- HCO_3^- is secreted into the capillary blood in exchange for Cl^-.
- The overall exchange of CO_2 for HCO_3^- in the capillary blood following a meal causes stomach venous blood to be more alkaline than the arterial blood (alkaline tide).
- K^+ and Cl^- passively diffuse through channels to the luminal fluid.
- Cl^- is the main anion of gastric fluid and the K^+ concentration is always higher than the plasma.
- Vomiting leads to a metabolic alkalosis and a hypokalemia. The hypokalemia is not the result of the body loss of K^+ but is caused by the alkalosis. However, chronic long-term vomiting can result in a significant loss of whole body K^+.

2. Peptic (Chief) Cells:

- Secrete pepsinogen, which is released from membrane-bound zymogen granules by exocytosis.
- Pepsinogen is a proenzyme that is initially activated by acid to the active protease pepsin. Pepsin can feed back and activate additional pepsinogen.
- Pepsin only operates in the acid medium of the stomach and begins the digestion of protein.
- Pepsin like salivary α-amylase is not a required enzyme for digestion.



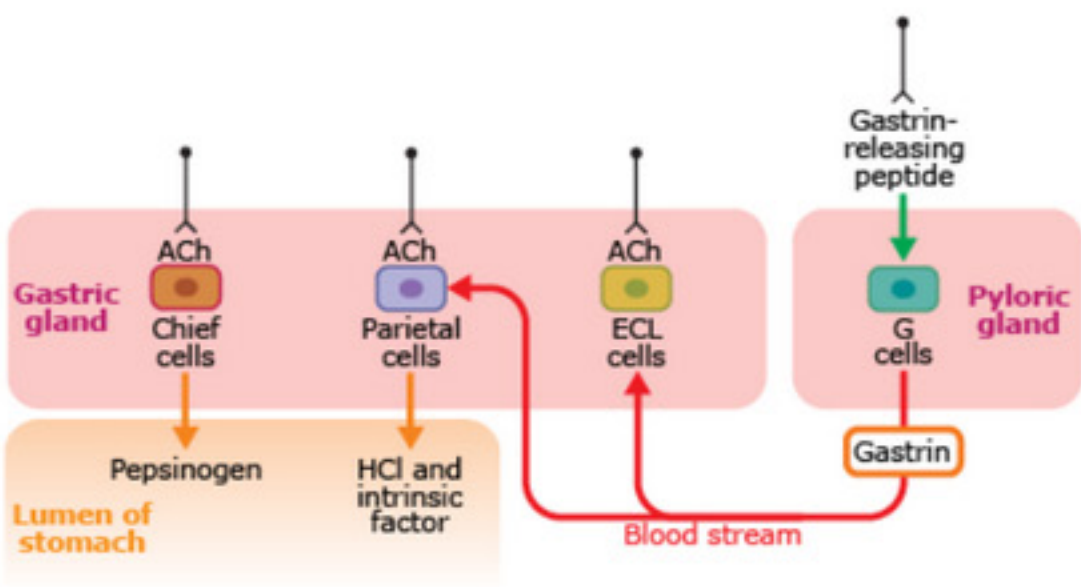
▲ **Figure 29–3.3C** Activation of Pepsinogen

3. Mucous Neck Cells:

- As with the surface epithelial cells, these secrete a protective solution.

3.3.3 Pyloric Glands

- Structurally similar to the gastric glands, but secrete a more viscous fluid with a protective function.



▲ **Figure 29–3.3D** Parasympathetic-Hormonal Interactions in Stomach Secretions

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3.4 Control of Gastric Secretions

Gastric secretion is divided into three phases:

1. Cephalic Phase:

- Begins with sight, smell, taste, and thought of food. Duration is short.
- Originates in the cerebral cortex, in the appetite centers of the hypothalamus and the amygdala. Directed by preganglionic fibers in the vagus nerve and postganglionic fibers that innervate gastric glands and *G cells*.
- Emotional state can exaggerate or inhibit the cephalic phase. Anger and hostility increase secretion. Anxiety, stress, and fear decrease secretion.

2. Gastric Phase:

- Begins with food entering the stomach. Duration can be hours.
- Stomach stretch initiates vagovagal reflexes, local enteric reflexes, and chemoreceptors releasing gastrin, which all contribute to the continued secretions.
- Increased motility and initiation of mixing waves.
- Homogenization and partial protein digestion of the chyme.

3. Intestinal Phase:

- The presence of chyme in the duodenum will continue to cause some gastric secretion. This may be caused by the duodenal release of gastrin.

The same factors originating in the duodenum that decrease stomach motility will also decrease gastric secretions via enteric reflexes, and acid in the duodenum releases secretin that decreases gastric secretions as well. In addition, a low-gastric-fluid pH decreases the secretion of gastrin. This is designed to prevent the stomach fluid's pH from declining below 2.0.

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4 The Small Intestine

4.1 Motor Functions

The contractile activity of the small intestine can be divided into mixing and propulsive movements.

Mixing Movements (Segmentation Contractions)

- Distension of the intestinal wall by the chyme elicits a localized concentric contraction, which segments the intestinal contents. It is said that they have the appearance of a chain of sausages. They chop and mix.
- Even though muscle stretch will initiate a segmental contraction, they are weak and ineffective unless the myenteric plexus is intact and functional.

Propulsive Movements (Peristaltic Waves)

- Consist of a contractile ring with a leading region of relaxation.
- The function is not only to propel the chyme toward the ileocecal valve but to produce a uniform distribution of chyme as it moves in a caudal direction. This action, coupled with contractions of the muscularis mucosae and villi, maximize the exposure of the chyme to the absorptive surface of the mucosa. In addition, the final digestion of carbohydrates and protein takes place on the mucosal surface just before absorption.
- The migrating myoelectric complex (MMC) is a unique propulsive wave of contraction. These waves only develop between meals with one about every 90 minutes. They begin in the stomach and with the pyloric and ileocecal sphincters relaxed, move undigested material into the colon. They are poorly understood but correlate with high plasma levels of motilin, a proposed hormone secreted by the small intestine.
- The MMC was originally considered a movement to sweep the GI tract clean between meals, but a more important function may be to prevent a backflow of colonic bacteria into the small intestine.

4.2 Intestinal Secretions

- Secretions of the mucosal epithelial cells have a dual purpose. They protect the surface epithelium and lubricate the chyme. The secretion of water and electrolytes assists in the absorption of nutrients, in part, by driving secondary active transport.
- Brunner glands, located in the first part of the duodenum, secrete an alkaline mucous fluid in response to irritation, parasympathetic stimulation, and secretin. Parasympathetic stimulation occurs concurrently with gastric secretions following a meal.
- Secretions by Brunner glands along with pancreatic secretions, which are high in HCO_3^-, protect the small intestinal lining from the caustic actions of acid and provide the necessary neutral environment for intestinal digestion and absorption. Rapid neutralization of acid is important. Even with the secretions of Brunner glands, the lining of the duodenum does not have the same level of protection against acid as the stomach.

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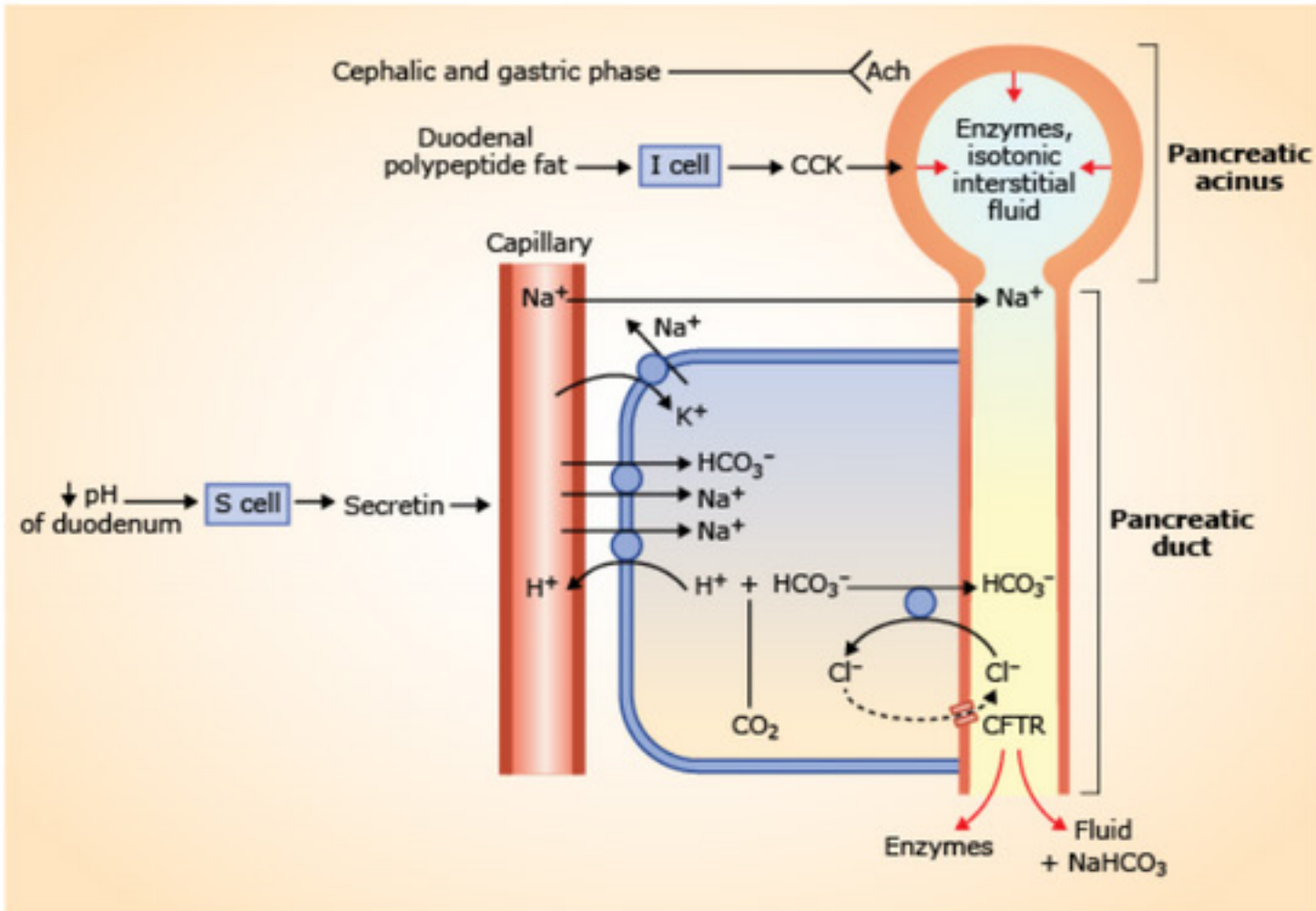
- Interestingly, sympathetic stimulation decreases Brunner mucus secretion and may provide this region with less protection from ulceration in highly emotional individuals.
- A mucus-type secretion is maintained throughout the length of the small and large intestine from goblet cells within the mucosa.
- The small intestinal mucosa is characterized by finger-like projections, the villi, and deep folds creating pits referred to as crypts of Lieberkühn. Deep within the crypts, enterocytes secrete an electrolyte solution similar to interstitial fluid. Secretion is via a chloride pump similar to that described for the acini of the salivary glands. This fluid, along with digested nutrients, is reabsorbed by the villi. Each cell of the villus has many microvilli, referred to as the brush border, which further increases the surface area. This cycle provides a watery environment for the final digestion and absorption of nutrients along the length of the small intestine.

4.3 The Pancreas

- Pancreatic secretions that enter the duodenum have two main functions:
  1. They represent the largest contributor of digestive enzymes to the gut.
  2. They provide HCO_3^- to neutralize stomach acid entering the small intestine.



▲ **Figure 29–4.3A** Composition of Pancreatic Secretions

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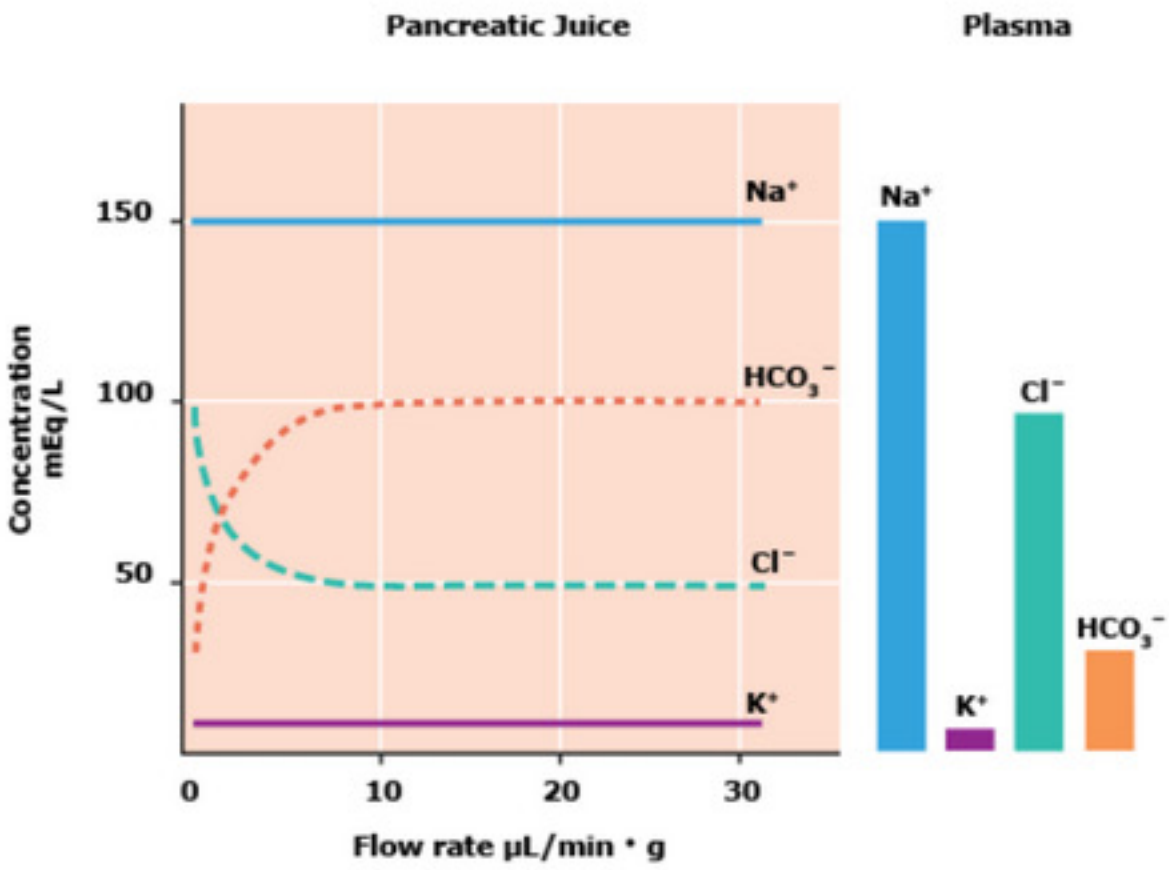
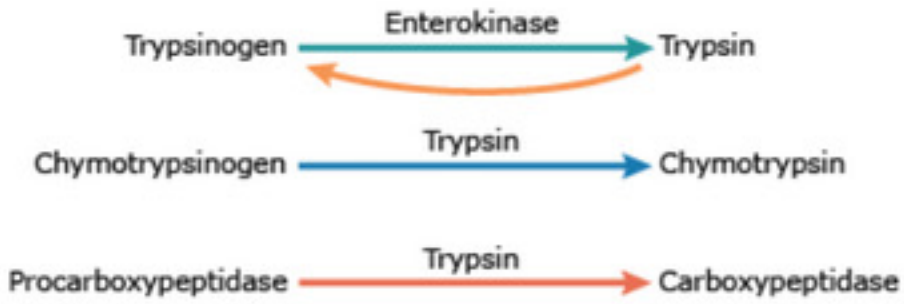


▲ **Figure 29–4.3B** Relationship Between the Composition of Pancreatic Secretions and Flow Rate

- Initial secretion into the acini is isotonic, with electrolyte concentrations similar to the interstitial fluid, plus a large number of enzymes and proenzymes (proteases).
- Acini secretion is stimulated by parasympathetic acetylcholine and CCK.
- *Note:* Pancreatic enzymes are required for the digestion of carbohydrate, fat, and protein, and their secretion is almost entirely due to CCK.
- Duct cells increase the fluid component and replace Cl^- with HCO_3^-.
- Duct cells are stimulated by secretin.
- Pancreatic enzymes include:
  1. α-amylase → CHO digested to mainly disaccharides
  2. Lipase → triglyceride to fatty acids and monoglycerides
  3. Cholesterol esterase → cholesterol hydrolysis
  4. Phospholipase A_2 → cleaves fatty acids from phospholipids
  5. Proteases are secreted in the inactive form along with a trypsin inhibitor to prevent activation. Initially, trypsin is activated by enterokinase/enteropeptidase, which is secreted by the intestinal lining. This creates the following cascade:



▲ **Figure 29–4.3C** Activation of Pancreatic Proteases

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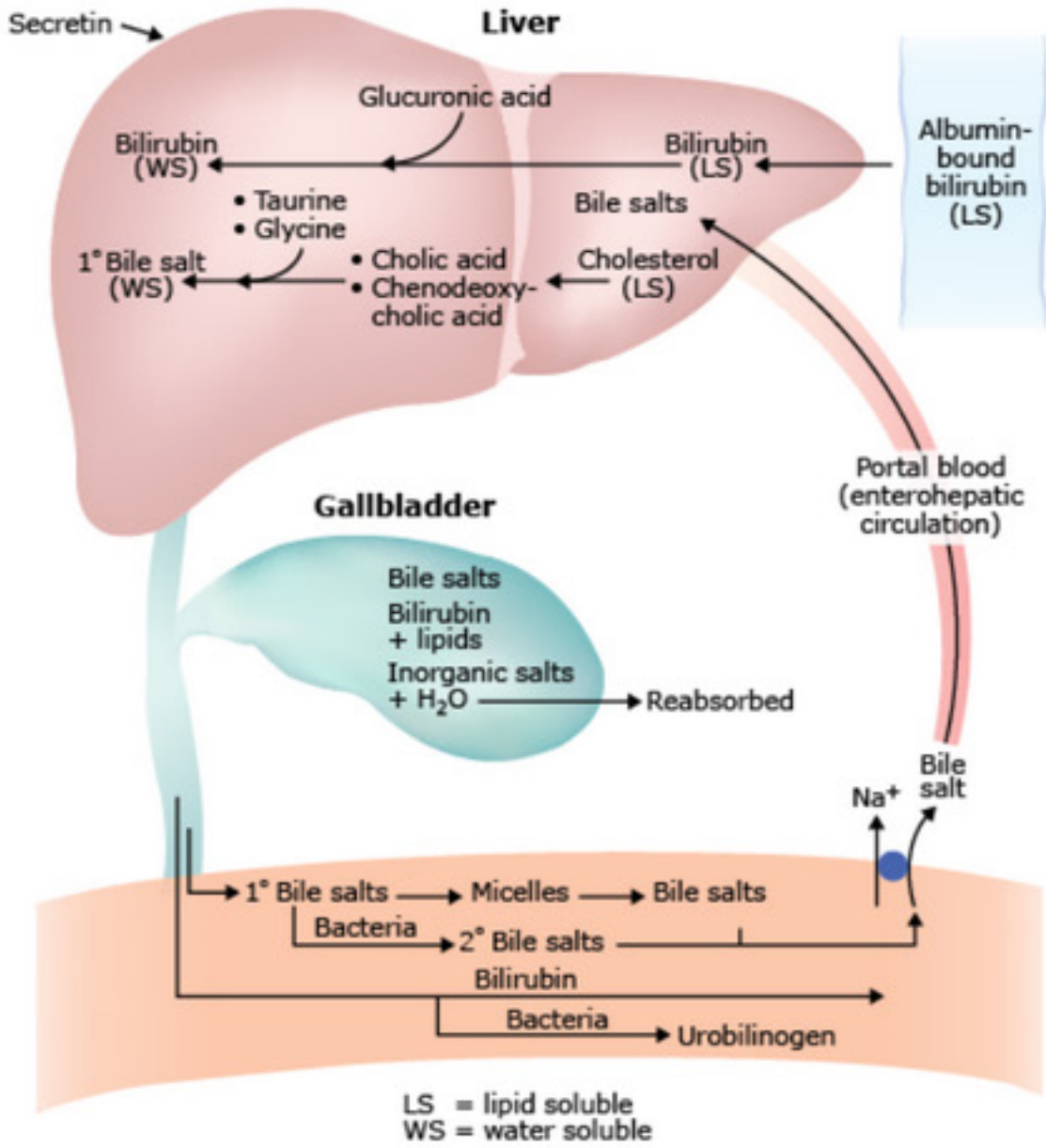
4.4 The Bile



▲ **Figure 29–4.4** Liver Production of Bile

- In addition to water and electrolytes, bile consists of two main components: bile salts and bile pigments.

4.4.1 Bile Salts

- Bile salts are synthesized by the liver from cholesterol, which is first converted to the lipid soluble bile acids, cholic acid and chendeoxycholic acid. The final step is the conjugation with taurine and glycine to form water-soluble bile salts. Those synthesized by the liver are called primary bile salts. Intestinal bacteria can slightly change their structure and they are then referred to as secondary bile salts.
- The conjugated form has a negatively charged, water-soluble head and a lipid-soluble tail.
- Bile salts have a detergent action on lipids, which reduces the size of the lipid particle and increases the surface area, facilitating digestion.
- In addition, when bile salts become concentrated, they organize into spherical micelles. The negative charge is on the outside and the lipid-soluble tail is directed inward.

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- Micelles are a vehicle to transport lipid material dissolved within their interior, and are important in the absorption of lipids.
- Absorption of lipid is completed in the ileum; in the distal ileum, micelles are disrupted and the bile salts are actively reabsorbed. Because only a limited supply is available following a meal they are often recycled several times, particularly after a fatty meal (enterohepatic circulation).
- The rate of synthesis of new bile salts is inversely related to the return of bile salts via portal blood.
- Because of their charge few are reabsorbed passively. *Note:* Only the distal ileum has the transporters (Na^+/bile salt cotransporter) to reabsorb the bile salts. A resection of the distal ileum results in the loss of bile salts in the stool. With a high-fat intake, fat can then appear in the stool.

4.4.2 Bile Pigments

- The main bile pigment is derived from bilirubin. It is an end product of hemoglobin metabolism in the reticuloendothelial system.
- The initially formed lipid-soluble bilirubin is transported to the liver attached to albumin.
- The liver conjugates the lipid-soluble bilirubin with glucuronic acid to form water-soluble bilirubin.
- The conjugated form cannot be reabsorbed from the intestine and thus is lost in the stool. However, some of the conjugated form is released from the liver into the bloodstream. It can appear in the urine.
- GI bacteria can convert bilirubin to urobilinogen. This form can be reabsorbed from the intestine and then resecreted into the bile or filtered by the kidney and excreted.

4.4.3 Salts and Water Components of Bile

- The liver is also a target tissue for secretin, which can increase the HCO_3^- component of bile.
- Within the gall bladder there is active reabsorption of sodium. Water and the remaining salts except Ca^{++} follow the sodium but bile pigments or bile salts cannot follow. The longer bile is in the gallbladder, the more concentrated the bile.
- The most potent stimulus to contract the gallbladder and relax the sphincter of Oddi is fat entering the duodenum releasing CCK.

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4.5 Digestion in the Small Intestine

4.5.1 Carbohydrates

- Complex carbohydrates consist mainly of the linked monosaccharides, glucose, galactose, and fructose.
- Carbohydrate digestion begins in the mouth with salivary α-amylase and continues in the proximal stomach until acid penetrates the bolus.
- Pancreatic α-amylase, a required enzyme, continues the digestion in the small intestine with disaccharides (sucrose, lactose) as the major end products along with small-branched α-limit dextrins and trioses.
- Disaccharides cannot be absorbed by the small intestine. Enzymes on the enterocytes covering the villi (sucrose, lactase, isomaltase) complete the digestion to the absorbable monosaccharides.
- Lactase can show a decline in some individuals after weaning, which results in *lactose intolerance*. As such, lactose continues to the colon, where it ferments and causes abdominal cramps, gas, and diarrhea. A bacterial-derived lactase can be taken in tablet form before ingesting dairy products.

4.5.2 Protein

- Protein digestion begins in the stomach with pepsin. Like salivary α-amylase, it is not a required enzyme and it only functions in the acid medium of the stomach. End products would include intact protein, polypeptides, and a few amino acids.
- Digestion continues in the small intestine with the pancreatic proteases, which are required enzymes. End products include short peptides and individual amino acids.
- As with carbohydrates, final digestion is accomplished on the enterocytes of the villi, which express peptidases. The end products include individual amino acids and very short peptides (di- and tripeptides), which are all readily absorbed.

4.5.3 Lipids

- The principle lipid in the diet is triglyceride. Lingual and gastric lipase release a few fatty acids but are not significant digestive enzymes.
- The stomach pulverizes triglyceride, increasing the surface area, but digestion really begins in the small intestine.
- Bile salts further emulsify the fat, and pancreatic lipase (required enzyme) digests the triglyceride to monoglycerides and fatty acids. Pancreatic colipase is a cofactor that permits lipase to function in a triglyceride bile salt mix.
- In addition, the pancreas secretes phospholipase A_2, which acts on phospholipids and a nonspecific cholesterol esterase.
- The monoglycerides and fatty acids (long chain) remain lipid soluble and are picked up by the micelles. However, because they are lipid soluble, they can be absorbed independent of bile salts and micelles. On the other hand, the fat soluble vitamins cannot be absorbed independent of the micelles.

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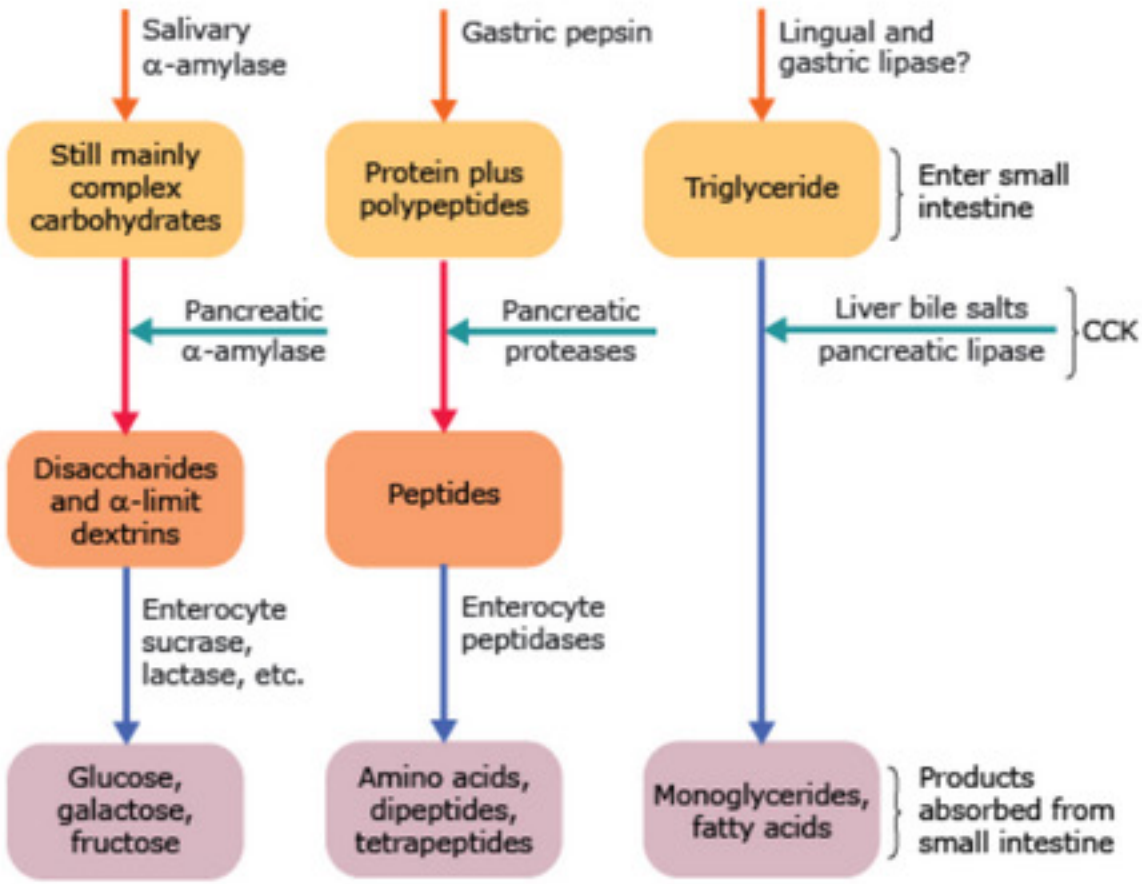
The following figure is a summary of digestion in the small intestine. *Note:* pancreatic enzymes are required for the digestion of carbohydrates, proteins, and fat. These enzymes depend on CCK for their release into the duodenum.



▲ **Figure 29–4.5** Overview of Digestion

4.6 Absorption from the Small Intestine

4.6.1 Carbohydrates

- Monosaccharides do not diffuse across cell membranes; protein carriers are required.
- Uptake is as illustrated in the accompanying figure. On the luminal membrane, glucose and galactose are transported by secondary active transport driven by the large sodium gradient established by the Na^+/K^+-ATPase pump.
- Electrolyte secretion by the enterocytes in the crypts maintains a constant delivery of sodium to drive the monosaccharide across the luminal membrane. As stated previously, luminal sodium stimulates the uptake of glucose and glucose stimulates the uptake of sodium. Fructose uptake is not linked to sodium.
- The preceding is utilized in a simple treatment for the cholera toxin, which acts to increase the electrolyte secretion by the crypt enterocytes. Oral administration of an electrolyte solution with glucose will accelerate the reuptake of fluid, reducing the associated diarrhea.
- Once across the luminal membrane, the high concentration of monosaccharides within the cell drives the passive facilitated transport (GLUT2) across the basolateral membrane.

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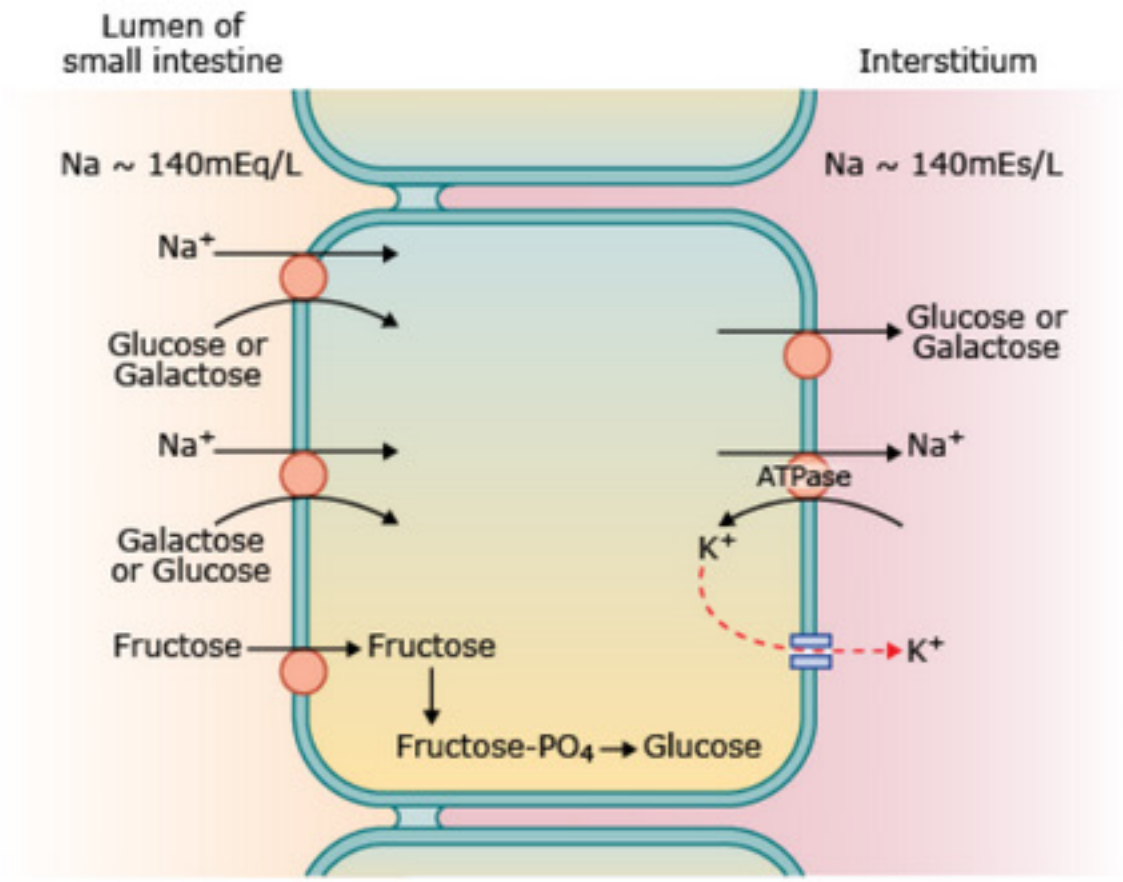

▲ **Figure 29–4.6** Absorption of Carbohydrates From the Small Intestine

4.6.2 Amino Acids and Peptides

- The initial uptake of amino acids across the luminal membrane is, as with glucose and galactose, a secondary active transport linked to sodium. Because of the great variety of amino acids, the carriers tend to be nonspecific.
- Di- and tripeptides are also readily absorbed but by a slightly different mechanism. Again, it is a symporter, but in conjugation with H^+ rather than sodium. Within the cell the peptides are digested to amino acids. The basolateral membrane has additional transporters for the amino acids.

4.6.3 Lipids

- The end products of triglyceride digestion are mainly monoglycerides and long-chain fatty acids. As they are lipid soluble, some diffuse into the enterocytes but most are taken up by the micelle along with other lipid materials, including the fat-soluble vitamins. Again, the micelle acts as a vehicle and transports lipids to the mucosal barrier. Uptake into the enterocytes is by simple diffusion.
- Once within the enterocytes, the monoglycerides and fatty acids are re-esterified to triglyceride and form lipid droplets, the chylomicrons.
- Chylomicrons are extruded to the interstitium by exocytosis but are too large to enter the systemic capillaries. Instead, they enter the villi central lacteal and then, via the lymphatic thoracic duct, enter the systemic circuit. Smaller-chained fatty acids, which are more water soluble, diffuse directly to the systemic capillaries.

Note: If the concentration of bile salts falls below that required for micelle formation, some lipid absorption still takes place, but fat soluble vitamins will not be absorbed.

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5 The Colon

5.1 Motor Functions

- The ileocecal valve prevents backflow of colonic contents into the small intestine. The valve protrudes into the cecum and pressure in the colon closes the valve.
- As with the small intestine, movements can be classified as mixing or propulsive.
- Mixing movements again are produced by circular contractions. These can be intense, almost occluding the colon. At the same time, the longitudinal strips of taenia coli contract, creating long, saclike bulges called haustrations.
- Propulsive movements are a type of peristalsis called *mass movements*. There is initially a constrictive ring then, distal to this, about 20 cm of colon contracts as a unit, propelling the fecal matter toward the anal region. Mass movements are aided by gastrocolic and duodenocolic reflexes following a meal.
- The colon terminates in the rectum, which lacks circular muscle and has only sparse longitudinal muscle. It acts as a reservoir to store fecal material before defecation.
- The rectum joins the anal canal surrounded by smooth and skeletal muscle. Thus, the alimentary tract is characterized by skeletal muscle at the beginning and end, and the reflex of swallowing and defecation involve reflexes that pass through the central nervous system.

5.2 Colonic Secretions

- The colon does not have digestive enzymes, nor does it have the transport proteins for absorbing the end products of carbohydrate or protein digestion. If they are not digested and absorbed in the small intestine, they pass into the stool. However, there is some fermentation due to the colonic bacteria, as with lactose intolerant individuals.
- The colon has the crypts of Lieberkühn, but there are no villi as in the small intestine. Distal segments mainly serve a storage function. Secretion is normally a mucus-type high in HCO_3^- that is protective and acts as an adherent for the fecal material.
- There continues to be a net reabsorption of electrolytes, particularly in the ascending and transverse colon. The colon is a target tissue for aldosterone whose actions are similar to that in the kidney. It promotes the reabsorption of NaCl and water but a net secretion of K^+. Some excess K^+ is lost by the colon but the main route of K^+ excretion is the kidney.
- Irritation of the colon lining often causes a much more serous type of secretion. The result can be a diarrhea with the loss of a large amount of water and electrolytes. Not only NaCl is lost, but K^+ and HCO_3^- is lost as well. The loss of HCO_3^- promotes a metabolic acidosis. This is often accompanied by a hyperkalemia but, in this case, the washout of K^+ promotes hypokalemia.

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Unit 10

Endocrinology

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1 General Characteristics

Hormones can be classified biochemically as peptides/proteins, catecholamines, iodothyronines, and steroid hormones. The peptides/proteins and the catecholamines have quite different functional characteristics from the iodothyronines and the steroid hormones. This is best illustrated in the differences between the water-soluble and lipid-soluble hormones.

1.1 Storage

- **Water Soluble:** Stored in vesicles which constitute a reserve that can be quickly mobilized. In some cases, a prohormone is stored along with an enzyme that clips off the active fraction. The active and inactive fraction are released in equal numbers (e.g., insulin, ACTH).
- **Lipid Soluble:** Except for thyroid hormones they are synthesized as required; thus, they are slow to mobilize.

1.2 Receptors

- **Water Soluble:** Cannot penetrate cell membranes; receptors are on the outer surface of the cell membrane. Intracellular action is carried out by second messengers (cAMP) that quickly modify intracellular enzymatic reactions.
- **Lipid Soluble:** Easily diffuse across cell membranes; main receptors in the cytoplasm or the nucleus. Gene expression and protein synthesis are required to carry out their actions, which creates a delay in their actions.

1.3 Transport

- **Water Soluble:** Generally circulate free, unbound in the plasma (exceptions are IGF-I and growth hormone) and, as such, generally have short half-lives (α to molecular weight).
- **Lipid Soluble:** Circulate bound to protein, albumin, and specific globulins synthesized in the liver; sex-hormone-binding globulin, corticosteroid-binding globulin, thyroid-hormone-binding globulin, vitamin-D-binding globulin. Binding produces long half-lives in the circulation (α to the affinity for the binding globulin, T_4 = 1 week).

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1.4 Steroid Hormone Plasma Equilibrium

Large percentage of total		Small percentage of total
Globulin-hormone	⟷	Free hormone

- **Free Hormone:** Considered the active form of the hormone in the plasma; diffuses to the intracellular receptors; regulated by negative feedback.
- **Total Hormone:** An index of the bound fraction in the plasma, not the free, active form. Varies with the plasma protein concentration. The bound form acts as a reservoir of circulating hormone, which can buffer acute changes in hormone secretion (e.g., circulating bound T_4 buffers the removal of the thyroid for several days).
- Estrogen can increase the liver production of binding protein, which raises the bound and total hormone in the circulation. Thus, during pregnancy, it is expected that the total T_4 increases but the free fraction being regulated remains in the normal range. Androgens and liver dysfunction have the opposite effect on the circulating bound fraction.

1.5 The Glycoprotein Hormone Family

- Includes, TSH, hCG, FSH, and LH.
- All are heterodimers with an α and a β subunit.
- The α subunits are the same; the four hormones differ only in the β subunits. The β subunit provides specificity but, in vivo, the α and the β subunits are required for activity.
- Large water-soluble molecules with fairly long half-lives in the circulation.

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2 Analysis of Hormone Levels

2.1 Plasma Sampling

- Only provides the circulating level at the time of sampling. When present, a circadian rhythm and a pulsatile secretion may result in a single sample not being representative of overall secretion.
- Cortisol is secreted in pulses and has a circadian rhythm with the low point late at night and the high point early in the morning. The late-night sample can be close to zero (falsely indicating hypocortisolism) and the value early in the morning in a range suggestive of hypercortisolism. Thus, 24-hour urine cortisol often is required as an index of overall secretion.
- Growth hormone is secreted in pulses, 70% of which occurs during the night. An early morning sample underestimates overall secretion. Growth hormone stimulates IGF-I secretion and IGF-I has a long half-life in the circulation. As such, the plasma level of IGF-I is usually a good index of overall growth-hormone secretion.
- TSH secretion is somewhat pulsatile, with a circadian rhythm, but a single sampling is still a fairly good index of overall secretion. The free T_4 is one of the most stable hormones in the circulation.

2.2 Urine Sampling

- Peptide hormones, like insulin, are not present in urine. Although filtered, they are reabsorbed in the proximal tubule.
- Catecholamines and their metabolites are easily measured in urine.
- Protein hormones do appear and can be measured in urine. hCG: Urine test for pregnancy; LH, in particular, and FSH peak just before ovulation.
- Steroid hormones' free fraction is filtered and appears in urine. As mentioned previously, 24-hour urine cortisol is an index of overall secretion.

2.3 Permissive Effects

- The effectiveness of some hormones is enhanced by the action of another, or the presence of one hormone also may be required for another hormone to exert its effects.
- Cortisol has a permissive effect on glucagon and both cortisol and T_4 have permissive effects on catecholamines.

Note: Without cortisol, glucagon cannot prevent hypoglycemia.

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3 General Pathophysiology

There are three general patterns: Hormone deficiency, hormone excess, and hormone resistance.

3.1 Hormone Deficiency

- Can result from a number of causes: Infection, inflammation, infarction, hemorrhage, autoimmunity.
- An autoimmune hypofunction develops slowly; 80% to 90% of the glandular tissue must be nonfunctional before obvious symptoms appear. Examples include type 1 diabetes, Hashimoto thyroiditis, and Addison disease.
- Autoimmume antibodies can be present years before symptoms appear.
- In the early development of type 1 diabetes, it is not uncommon to develop symptoms of hyperfunction. In Addison disease, symptoms may first appear in a stressful situation.
- A stimulation test reveals a hormone deficiency.
- Insulin-induced hypoglycemia is a very sensitive test for the reserve of a stress hormone (cortisol, glucagon, growth hormone, and catecholamines), but it is not without risk. Better choices would include ACTH stimulation test for cortisol, and arginine infusion for growth hormone.

3.2 Hormone Excess

- Caused by tumors, hyperplasia, and autoimmune stimulation.
- Unlike autoimmune hypofunction, autoimmune hyperfunction develops rapidly; for example, Graves disease.
- Tumors can be functional (secreting) or nonfunctional.
- The posterior pituitary, a collection of nerve endings; unlikely to develop secreting tumors.
- Functional tumors are not completely resistant to feedback regulation (e.g., pituitary hypersecretion) of ACTH (Cushing disease); responds to high-dose dexamethasone, pituitary hypersecretion of growth hormone (acromegaly) responds to somatostatin but not hyperglycemia.
- Ectopic site oversecretion, usually peptide hormones, are never suppressible (e.g., ACTH, ADH, and PTH-related peptide).
- Suppression test for diagnosis.

Note: 24-hour urine cortisol replaces dexamethasone suppression test in most cases, but the low-dose and high-dose dexamethasone test will still appear on Step 1.

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3.3 Hormone Resistance

- In most cases, hormone resistance involves a water-soluble hormone.
- Can be a receptor failure or a post-receptor intracellular signaling pathway problem.
- Receptor system often is saturated, thus the plasma level of the hormone is not a good index of hormonal activity (e.g., type 2 diabetes).
- Characteristically, there are normal or elevated plasma levels of the hormone but with clinical signs of hormone deficiency and a failure of hormone replacement to correct the problem.
- Tissue resistance to PTH = plasma ↑ PTH, ↓ Ca, ↑ PO_4; in nephrogenic diabetes insipidus an injection of ADH will not reverse the diuresis.
- Reducing the elevated circulating levels of the hormone can return some receptor sensitivity. In fact, simply the presence of chronic high levels of a hormone, particularly a peptide hormone, can induce tissue resistance.
- Testicular feminizing syndrome—high circulating levels and tissue resistance to androgens but peripheral conversion of the androgen to estrogen will induce feminizing symptoms (estrogen receptors still functional).

3.4 Glandular Size and Function

- When an endocrine secreting tissue does not receive its normal input stimulus, it undergoes a reversible atrophy.
- An adenoma of an adrenal gland oversecreting cortisol suppresses ACTH and causes a decrease in the size of the contralateral adrenal. In both adrenals, the *zona fasciculata* and *zona reticularis* will atrophy. Removal of the functional adenoma can induce a hypocortisolism because, although the atrophy is reversible, it is a time-dependent process. Chronic treatment followed by sudden withdrawl of high doses of glucocorticoids will have a similar effect.
- Overstimulation of endocrine tissue can cause a hypertrophy, or hyperplasia, or both.
- In Graves disease, the autoimmune overstimulation of the thyroid induces a goiter.
- In renal failure, the hyperphosphatemia induces a hypocalcemia and a secondary hyperparathyroidism, a consequence of which is hyperplasia of the parathyroids.

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4 Hormonal Feedback

- There generally are two types of negative feedback:
  1. Physiological response-driven feedback (e.g., blood glucose) is the main factor controlling the secretion of insulin and glucagon.
  2. Endocrine axis-driven feedback (e.g., plasma cortisol suppresses the secretion of ACTH and CRH.
- In some cases, negative feedback is weak or absent. IGF-I and glucose suppress the secretion of growth hormone, but it is a weak effect. Nocturnal pulsatile release of growth hormone is unaffected by the negative feedback effects of glucose. There is little if any feedback in the control of prolactin secretion.
- Positive feedback does occur but is poorly understood. Low levels of estrogen inhibit but high levels stimulate the secretion of LH (creates the LH surge). At the pituitary high, estrogen levels increase the sensitivity of the gonadotrophs to GnRH by increasing the receptor levels and increasing post-receptor signaling pathways.

▲ **Figure 30–4.0** Response-Driven Feedback and Axis-Driven Feedback

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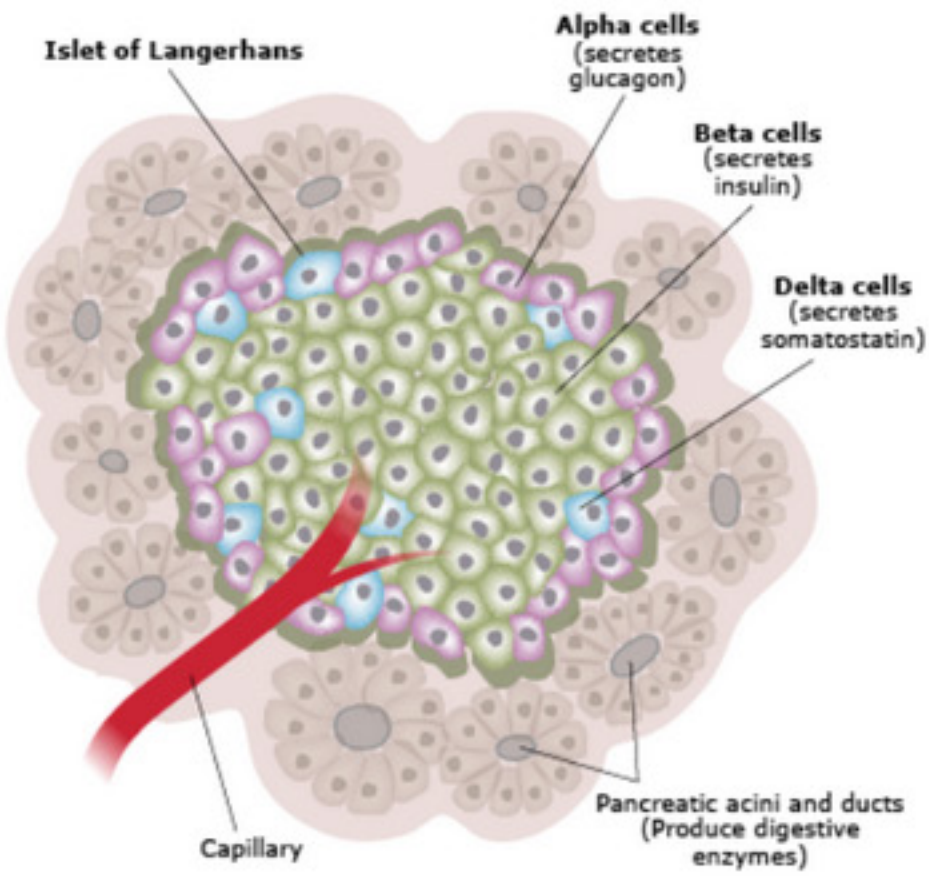
1 The Pancreatic Islet Cells



▲ **Figure 31–1.0** Pancreatic Islets

1.1 Beta Cells

- Constitute 75% of the islet cells and are located in the center of the islets.
- Proinsulin along with protease are packaged in the golgi apparatus. The protease then split the proinsulin, releasing the C peptide (connecting peptide of the α and β chains) and the active insulin.
- Equal quantities of insulin and C peptide molecules are released.
- Blood flow to the islet is first delivered to the islet center. Blood carrying the insulin is then delivered to the alpha and delta cells in the periphery before being released into the portal circulation. Insulin inhibits the release of glucagon from the alpha cells.
- Liver removes 50% of the secreted insulin on its first passage. No C peptide is removed by the liver.
- C peptide has no known function, but it serves as a marker of endogenous insulin secretion. Because it is not removed by the liver, C peptide is a better marker for insulin secretion than insulin itself.

Insulin injection—suppresses endogenous insulin secretion → hypoglycemia, C peptide is low

Insulin secreting tumor → hypoglycemia, but C peptide is high

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- Half-life of insulin is five to eight minutes, that of C peptide is three to four times longer.
- Insulin's overall function is the storage of ingested nutrients. The three tissues specialized for storage and the main insulin targets are liver, skeletal muscle, and adipose tissue.

1.2 Alpha Cells

- Constitute about 10% of the islet cells and are located around the periphery of an islet.
- Glucagon released into the portal circulation is about 80% extracted by the liver.
- The only significant target for glucagon is the liver. Skeletal muscle is not a target tissue for glucagon. (*Distractor:* Glucagon causes glycogenolysis in skeletal muscle.)
- Half-life of glucagon similar to that of insulin.
- Glucagon's main action is to promote liver glycogenolysis but it also promotes gluconeogenesis. It is the main hormone involved in raising plasma glucose.

1.3 Delta Cells

- Constitute a very small percentage of the islet cells and, like the alpha cells, are located at the periphery of an islet.
- Release somatostatin, but it only has a local inhibitory effect on the alpha cells.
- Stimuli that release somatostatin are similar to those that release insulin.
- Thus, following a mixed meal, the secreted somatostatin and the insulin delivered to the alpha cells suppress the secretion of glucagon.

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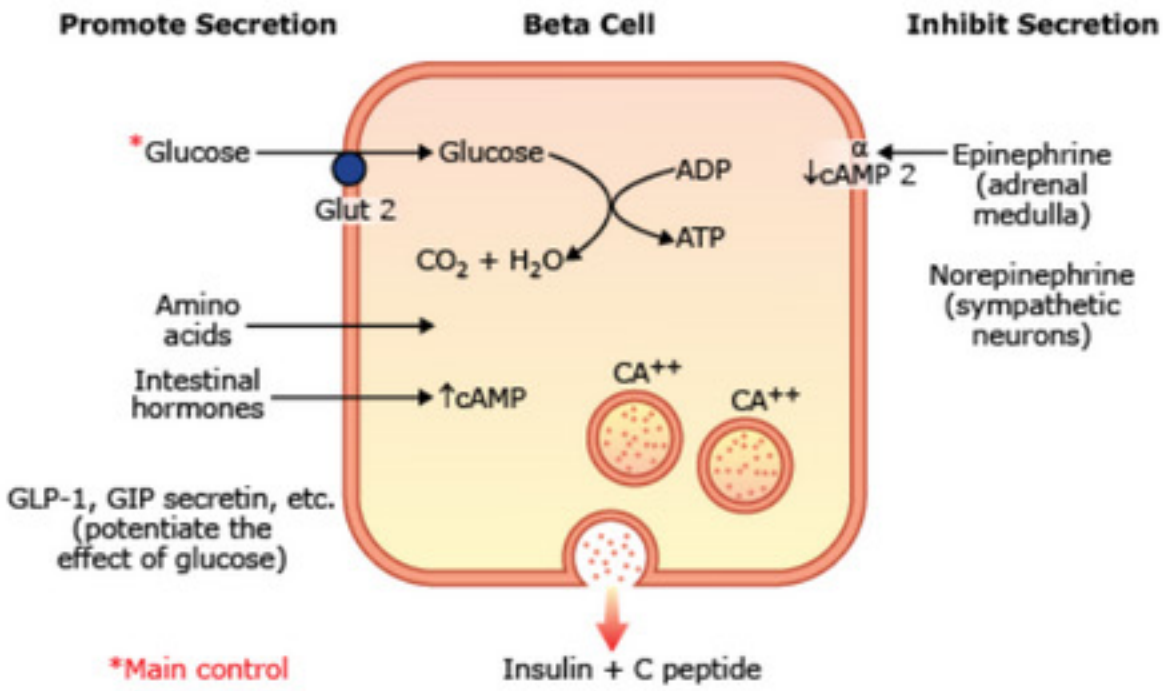
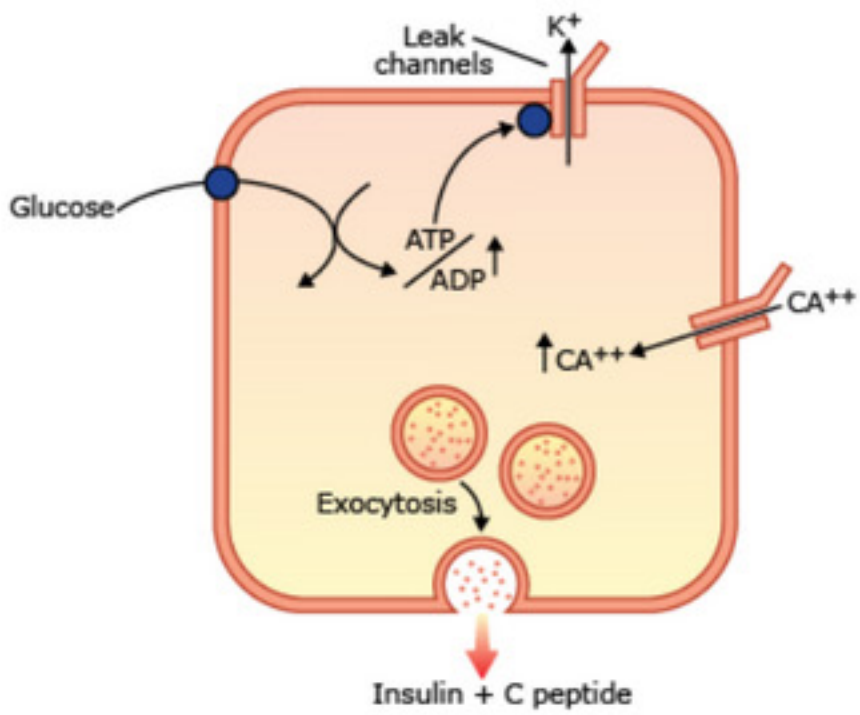
2 Control of Insulin and Glucagon Secretion

2.1 Insulin Secretion



▲ **Figure 31–2.1A** Control of Insulin Secretion



▲ **Figure 31 –2.1B** β Cell Insulin Release

- The metabolism of glucose increases the ATP/ADP ratio.
- ATP-sensitive (ligand-gated) K^+ channels close. Sulfonylurea drugs also close these channels.
- Depolarization of the membrane activates (opens) voltage-gated Ca^{++} channels in the membrane.
- The influx of Ca^{++} triggers the release of insulin and C peptide bound in vesicles.
- 2-Deoxyglucose prevents the metabolism of the glucose and thus prevents the release of insulin.

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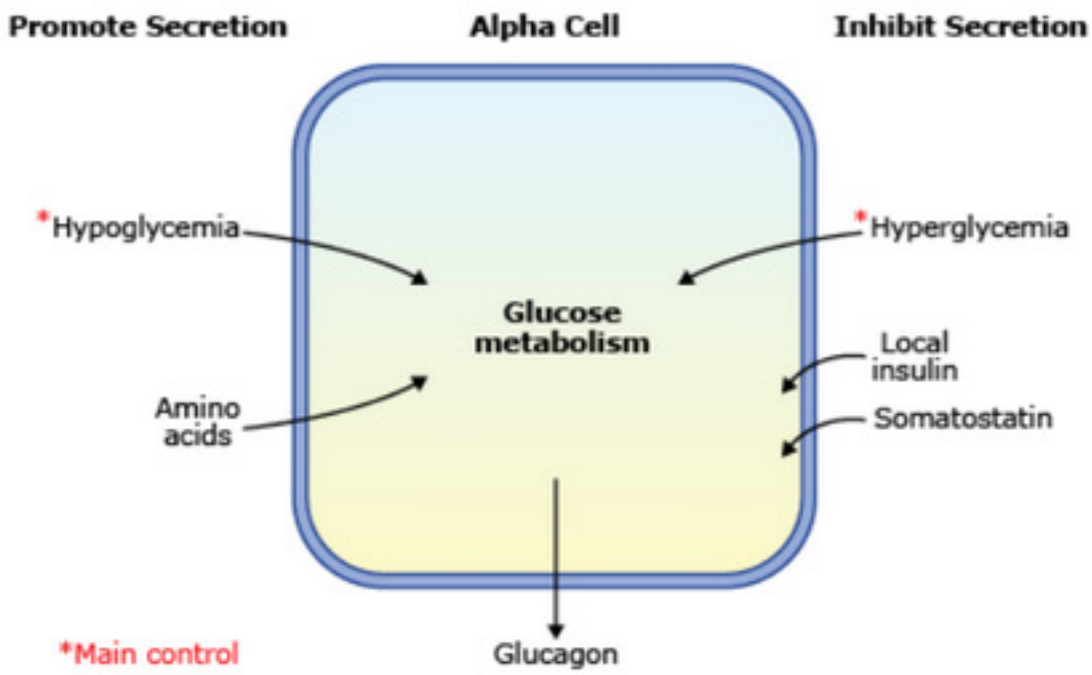
2.2 Glucagon Secretion



▲ **Figure 31–2.2** Control of Glucagon Secretion

2.3 Overall Control

- The main controlling factor in the secretion of both insulin and glucagon is plasma glucose.
- Amino acids release insulin and glucagon. The CHO/protein content of the meal determines the rate of insulin to glucagon release (insulin/glucagon ratio). A mixed meal high in CHO releases mainly insulin. A high-protein meal releases mainly glucagon. This is to protect the individual from the hypoglycemic effects of insulin following a protein meal.
- The I/G ratio determines the net flow of hepatic metabolic pathways. A high ratio signal promotes glycogen synthesis, and the excess glucose is converted to fat.
- Liver takes up glucose via GLUT2 transporters (insulin independent).
- The α_2 inhibition of insulin secretion, which is activated by catecholamines, protects against the hypoglycemic effects of exercise.
- Because gut hormones potentiate the effect of glucose on the beta cells, oral glucose gives a greater insulin response than intravenous glucose.

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2.4 Counterregulatory Hormones

Insulin promotes the storage of nutrients and inhibits the breakdown of glycogen, protein, and triglyceride. Stress hormones do the opposite; they mobilize substrates. All the stress hormones have one uniform effect, which is to act to raise plasma glucose. This is referred to as a counterregulatory response, and all stress hormones are classified as counterregulatory hormones. Stress, substrate mobilizing hormones include:

- **Growth Hormone:** Decreases the peripheral uptake of glucose (anti-insulin response) and promotes lipolysis
- **Glucagon:** Glycogenolysis, gluconeogenesis in liver
- **Cortisol:** Decreases the peripheral uptake of glucose (anti-insulin response), gluconeogenesis, proteolysis, and lipolysis
- **Catecholamines:** Glucogenolysis, lipolysis

Note: The most sensitive test for the reserve of a stress hormone is an insulin-induced hypoglycemia. However, permission is often difficult to get through a human studies committee, particularly for hospitalized patients.

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3 Specific Actions of Insulin

- **Insulin Receptor:** Member of the receptor tyrosine kinase family. A high-yield topic but the details are presented in biochemistry. One important action of insulin is to insert GLUT4 transporters in adipose tissue and resting muscle. Without the aid of insulin, these tissues cannot take up glucose. However, exercising muscle does not require insulin for glucose uptake. GLUT2 transporters (e.g., beta cells and liver) are insulin independent.
- **Carbohydrate Metabolism:** In all tissues, when glucose is made more available its metabolism to CO_2 and H_2O increases (i.e., greater utilization of glucose as a source of energy). Insulin specifically promotes the synthesis and storage of glycogen and inhibits glycogen breakdown in liver and skeletal muscle. An insulin deficiency elevates glucagon, which does the opposite.
- **Protein Metabolism:** Increases tissue uptake of amino acids, promotes protein synthesis, and inhibits proteolysis. An insulin deficiency promotes proteolysis and a negative nitrogen balance.
- **Triglyceride Metabolism:** Promotes the clearance of triglycerides from the circulation and triglyceride synthesis. It decreases lipolysis by inhibiting hormone-sensitive lipase. Insulin deficiency increases the activity of hormone-sensitive lipase and lipolysis.

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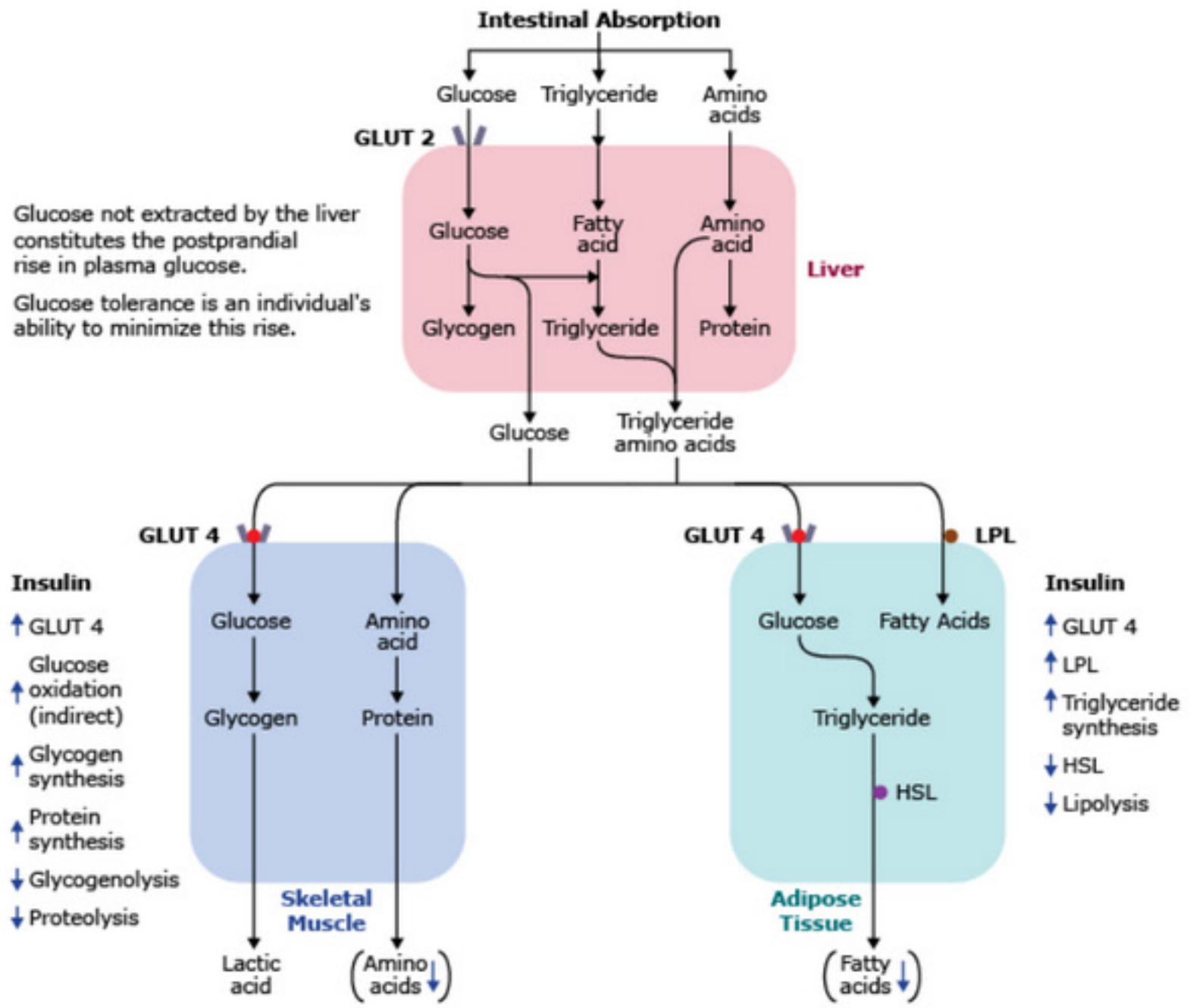

LPL—lipoprotein lipase—an extracellular lipase that clears triglyceride from the circulation.

HSL—hormone-sensitive lipase—an intracellular lipase that promotes lipolysis inhibited by insulin, activated by all stress hormones.

▲ **Figure 31–3.0** Peripheral Actions of Insulin

- **Plasma Potassium:** Aldosterone is considered to be the chronic regulation of ECF potassium, but insulin and catecholamines are considered the acute regulation. In the acute regulation, insulin is considered the most important. Insulin pumps ECF potassium following a meal into non-vital tissues (insulin's target tissues) via the Na/K-ATPase pump and Na/K symporters. The postprandial rise in potassium is greater in diabetes mellitus, and injection of insulin (plus glucose) can be given to prevent life-threatening hyperkalemia.

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4 Diabetes Mellitus

- Diabetes is preceded by a phase of glucose intolerance.
- Type 1 is the result of complete or almost complete insulin deficiency.
- Type 2 is a heterogenous group of disorders with variable levels of insulin resistance, impaired insulin secretion, and elevated glucose production.
- The terms insulin-dependent and insulin-independent diabetes are outdated.
- Age criteria also is not appropriate in the classification. Type 1, early onset can develop later in life. Type 2 adult onset appears frequently in obese adolescents.
- Diagnosis based on glucose intolerance:

Fasting glucose	< 100 mg% normal
	100–125 mg% impaired glucose control
	>125 mg% diabetes or
	diabetes = >200 mg% 2 hrs after a 75 mg oral glucose load

- Levels of hemoglobin A1C are not recommended for diagnosing diabetes but remain the preferred method for monitoring the effectiveness of diabetes treatment.
- Stress (counterregulatory) hormones in some cases can promote diabetes and, at the very least, aggravate the hyperglycemia of diabetes.
- Glucose intolerance can develop in late pregnancy. Human placental lactogen (hPL) acts similarly to the stress effects of growth hormone. More specifically, human placental lactogen decreases the peripheral uptake of glucose. Most women revert to a normal glucose tolerance following delivery but have a higher risk of developing diabetes later in life.

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4.1 Type 2 Diabetes

- Insulin resistance, impaired insulin secretion, excessive hepatic glucose output, and abnormal fat metabolism.
- Insulin resistance usually precedes an insulin secretory defect, but diabetes only develops when insulin secretion becomes inadequate to overcome the resistance.
- Initial insulin resistance with normal glucose tolerance occurs because of increased insulin secretion; following this, hyperinsulinemia is reduced and increased postprandial glucose with increased hepatic glucose output leads to diabetes.
- Receptor sensitivity is reduced, but post-receptor signaling is probably the main defect.
- Plasma insulin can be elevated, normal, or below normal.
- Decreased insulin response on target tissues, including liver, skeletal muscle, and adipose tissue, but glucose metabolism (CO_2 and H_2O) is unaffected.
- Three main underlying problems:
  1. Inability to increase GLUT4 mediated glucose uptake, especially in skeletal muscle.
  2. Decreased ability of insulin to suppress hepatic glucose production and output. Liver makes glucose by glycogenolysis in the short term and by gluconeogenesis in the long term.
  3. Inability to suppress hormone-sensitive lipase or increase the activity of lipoprotein lipase in adipose tissue.
- Liver: ↑ gluconeogenesis, ↓ glycogen, → increased glucose output.
- Adipose tissue: ↓ triglyceride uptake, ↑ FFA output.
- Strong genetic component.
- Obesity, especially visceral or central, is very common.
- These individuals tend to be ketosis-resistant. Having some endogenous insulin production may protect the individual from developing ketoacidosis.
- Type 2 individuals tend to have the highest plasma glucose levels. Diabetic coma is associated with the hyperglycemia, not the ketosis; thus, coma is more likely to develop in a person with type 2.

4.2 Type 1 Diabetes

- Results almost exclusively from islet-directed autoimmunity taking place over months or years.
- May be triggered by an infectious stimulus.
- Initial effect can be an oversecretion of insulin.
- Must have approximately 80% of the beta cells destroyed before overt symptoms of diabetes appear.
- Ketosis prone.
- Antibodies are present and can be assayed during development of the disorder, but not after complete destruction of the beta cells.
- Other pancreatic islet cells are unaffected (alpha cells maintain glucagon secretion). Even though plasma glucose is elevated, plasma glucagon also is elevated.

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4.3 Acute Consequences of Diabetes Mellitus

- Hyperglycemic, hyperosmolar state, diuresis with dehydration, possibly hypotension and tachycardia, and possible ketoacidosis or hyperosmotic coma.

4.3.1 Plasma Laboratory Abnormalities

- Hyperosmolar state due to elevated glucose. Plasma Na^+ concentration is normal or slightly below normal. Whole-body sodium is significantly reduced due to the diuresis and dehydration. Twice the Na^+ concentration is not a good index of plasma osmolarity.

Effective osmolarity = $2(Na^+)$ + (glucose mg/dL divided by 18)

- Potassium shifts from the intracellular to the extracellular fluid for three reasons:
  1. If there is an acidosis, H^+ enters the cells to be buffered driving K^+ to the extracellular fluid to maintain electrical neutrality.
  2. Hyperosmotic state shrinks cells, driving the K^+ with the water to the extracellular fluid.
  3. The lack of the normal effect of insulin pumping K^+ into cells.
- Plasma K^+ concentration can be slightly elevated, normal, or below normal, depending on the diuresis. Even if the plasma K^+ is normal, there is a whole-body deficit in K^+, and K^+ replacement usually is required during treatment.
- Insulin replacement with plasma K^+ below normal can cause severe hypoglycemia.
- Elevated plasma BUN and creatinine due to volume depletion.

4.4 Renal Response

- Glucose acts as an osmotic diuretic because it fails to be completely reabsorbed in the proximal tubule. This results in greater back diffusion of water and electrolytes (Na, K, Cl) in this segment.
- An overload is delivered to the loop of Henle and distal segments, and the diuresis results in significant losses of fluid, glucose, and major electrolytes.
- Even in the presence of elevated ADH, a concentrated urine cannot be formed due to the high flow through the loop of Henle. This diminishes the interstitial osmolar gradient in the renal medulla.
- A diabetic often is said to form a large volume of dilute urine. It is very dilute in terms of electrolytes, but the large volume causes a significant loss of whole-body electrolytes.
- If a ketoacidosis is present, the urine pH will be low and ketone bodies lost in an acid urine act as titratable acid.

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4.5 Diabetic Ketoacidosis

- The fatty acids released by adipose tissue are delivered to the liver. In the absence of insulin, but high glucagon, there is a shift toward ketone body synthesis.
- At physiological pH ranges, ketone bodies exist as ketoacids producing a metabolic acidosis with a widening of the anion gap.
- Arterial pH ranges from 6.8 to 7.3 and bicarbonate can be as low as 10 mM.
- Electrolytes as previously stated, along with dehydration.
- Respiratory compensation results in rapid deep breathing (Kussmaul breathing) and a fruity odor.
- Treatment involves fluid replacement (saline), administration of insulin, and potassium replacement as needed.
- The major metabolic complication of diabetic ketoacidosis is cerebral edema, which most often develops in children.

4.5.1 Hyperglycemic Hyperosmolar State

- Hyperosmolarity, dehydration, hypotension, tachycardia, mental confusion, lethargy, or coma.
- Most often develops in a type 2 diabetic; blood glucose can be as high as 1200 mg%.
- Acidosis mild or absent; no Kussmaul breathing.
- Initial diuresis leads to dehydration and then lower urine flows, which aggravate the hyperglycemia.

4.6 Chronic Complications of Diabetes

- Microvascular complications in type 1 and type 2 diabetes, and are due to the hyperglycemia.
- **Diabetic Retinopathy:** Retinal microaneurysms and hemorrhages leading to retinal ischemia, which may lead to retinal detachment.
- **Nephropathy:** Initially, structural changes in the efferent arteriole lead to glomerular hypertension and an increased GFR. Treatment: ACE inhibitors. The progression is then toward a normal GFR, followed by a microalbuminuria. Can be followed by nephrotic syndrome. Finally, it can result in loss of nephron function and end-stage renal disease.
- **Atherosclerosis:** Increased risk in large- and medium-sized vessels—peripheral vascular disease and amputation.
- **Neuropathy:** Occurs in about 50% of those with long-standing diabetes—clinical features similar to other neuropathies.

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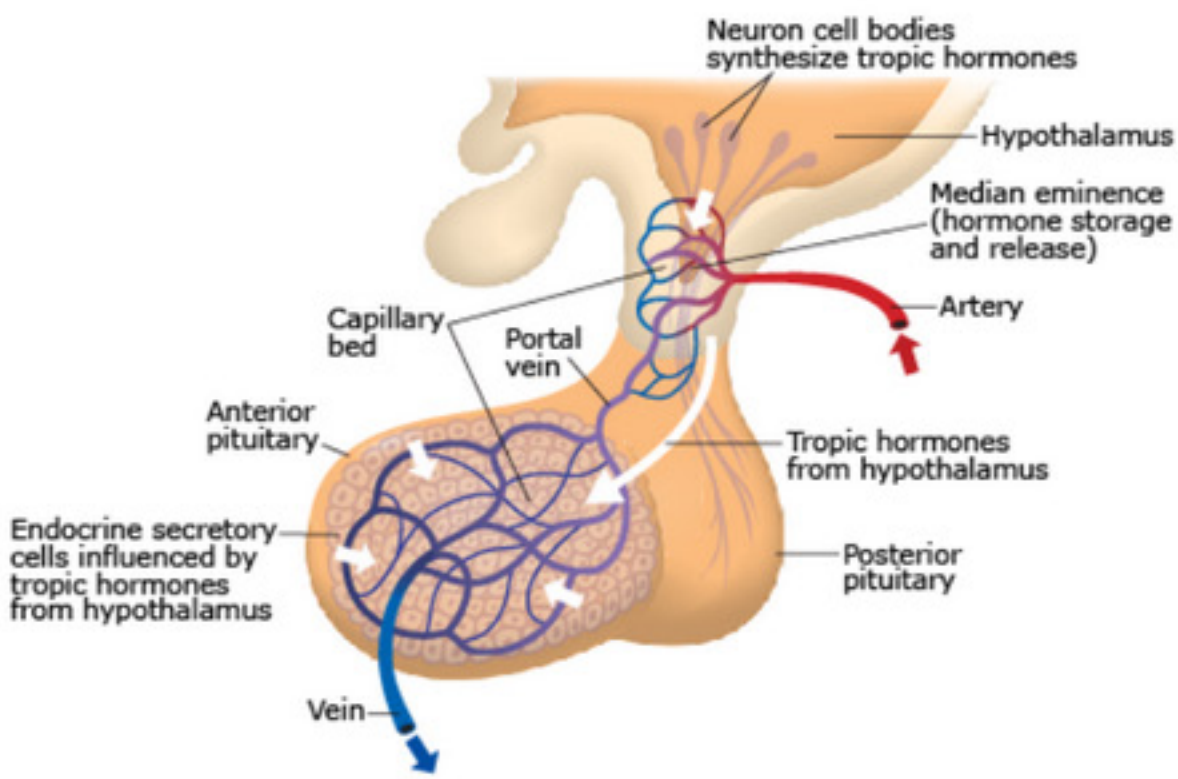
1 General Characteristics

- The anterior pituitary is located in the sella turcica, a depression of the sphenoid bone sealed off from the brain by a membrane. Incompetence of the membrane allows cerebrospinal fluid to enter, compressing the anterior pituitary (empty sella syndrome) but pituitary function usually is normal.
- The optic chiasm is 5–10 mm above the diaphragm.
- Tumors of the anterior pituitary have only one way to go, toward the brain. Typical symptoms are headache and visual problems (bitemporal hemianopia).
- Hypothalamic hormones are synthesized by neurons. A neuron synthesized hormone is always a water-soluble hormone. It is synthesized in the neuron cell body, packaged in vesicles, and transported to the nerve terminals where it is stored and released.
- The hypothalamic axons converge on the median eminence region of the hypothalamus. Hormones are released into the portal circulation and transported to the anterior pituitary.
- The hypothalamic-anterior pituitary hormones are released in pulses. In the thyroid system, the pulses are generally smaller and the longer half-life of TSH creates a fairly stable plasma level.
- The gonadotrophs of the anterior pituitary require a pulsatile input to prevent down-regulation of its receptor system. Although a constant infusion of GnRH initially increases the secretion of LH and FSH, with time, secretion diminishes below normal.



▲ **Figure 32–1.0A** Hypothalamic-Anterior Pituitary System

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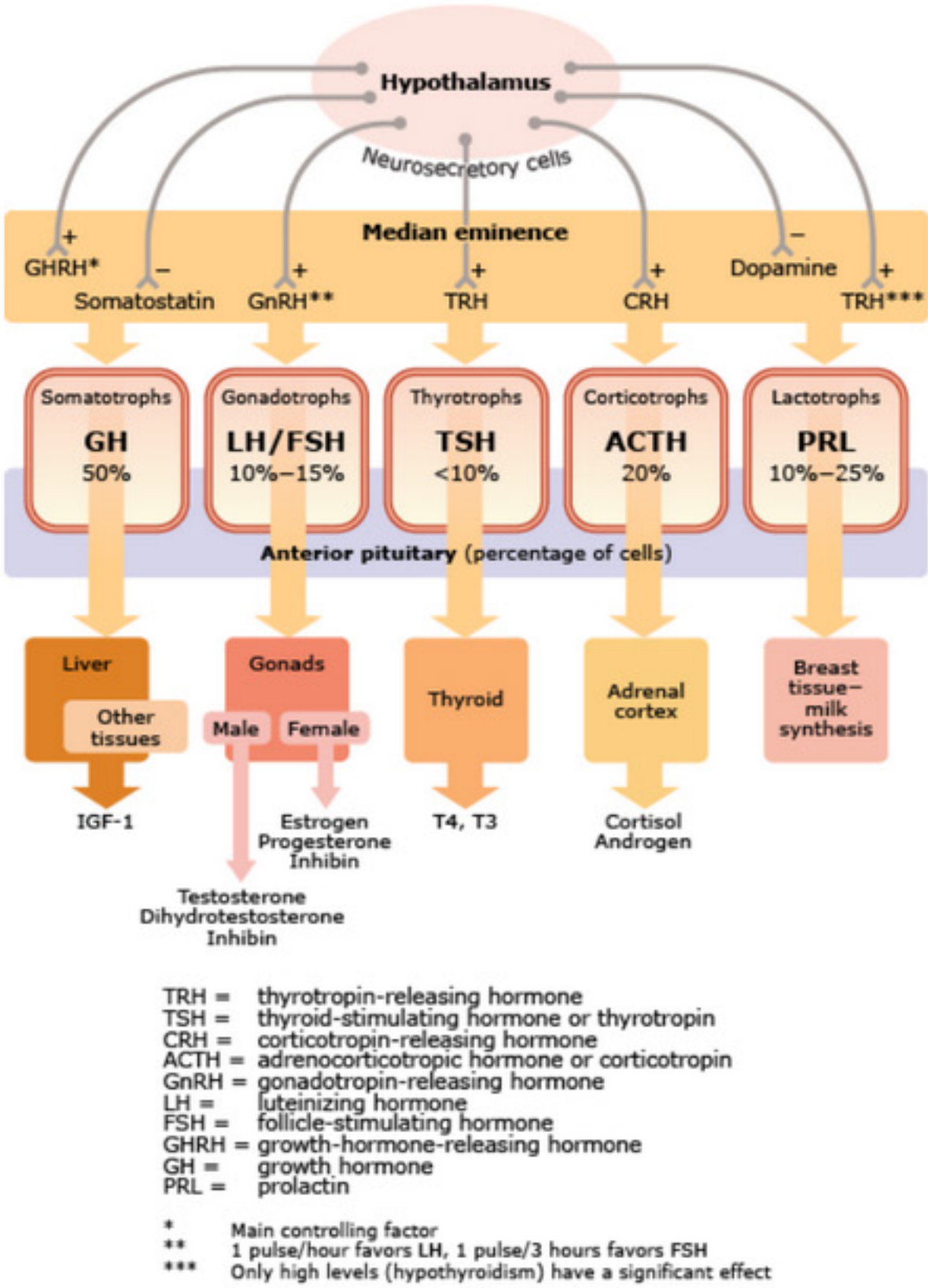

TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone or thyrotropin
CRH = corticotropin-releasing hormone
ACTH = adrenocorticotropic hormone or corticotropin
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone
FSH = follicle-stimulating hormone
GHRH = growth-hormone-releasing hormone
GH = growth hormone
PRL = prolactin

* Main controlling factor
** 1 pulse/hour favors LH, 1 pulse/3 hours favors FSH
*** Only high levels (hypothyroidism) have a significant effect

▲ **Figure 32–1.0B** Hypothalamic-Anterior Pituitary Hormones

Somatotrophs: growth hormone = somatotropin. Growth hormone, human placental lactogen, and prolactin are similar. Growth hormone can act as an agonist for the prolactin receptor.

Lactotrophs: Prolactin circulates unbound, and in the basal state the plasma levels are the same in men and women. Increased release in response to stress and during sleep. Prolactin is not involved in breast development during puberty but is involved in breast enlargement during pregnancy. Hyperprolactinemia causes hypogonadism. It disrupts the GnRH-gonadotropin axis but does not affect the basal levels of LH and FSH.

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2 Pathophysiology

2.1 Hypopituitarism

- **Hypothalamic Dysfunction (Kallmann Syndrome):** Result of defective GnRH synthesis (tertiary hypogonadism). A genetic disorder that prevents the embryonic migration of GnRH neurons from the olfactory region to the hypothalamus.
- **Craniopharyngioma:** Slow-growing tumors that arise from cells near the pituitary stalk. Usually develop in children. Symptoms include headache and bitemporal hemianopia. Tumor damage to the pituitary stalk often causes a deficiency in gonadotropins, growth hormone, and ADH. Additional problems can include suppression of other pituitary hormones, except prolactin, which may increase.
- Panhypopituitarism can be the result of a large number of etiologies, including the mass effect of macroadenomas, infarction, hemorrhage, and infiltration.
- Often presents as a sequential loss of hormone function: Gonadotropin and growth hormone, then TSH, ACTH, and, in the end, prolactin. The main problem in panhypopituitarism is the loss of cortisol from the adrenal gland (zona faciculatus-reticularis not zona glomerulosa).
- Isolated deficiencies include growth hormone and gonadotropins but rare for TSH, ACTH, or prolactin (TAP). The loss of any TAP usually is associated with panhypopituitarism.

Trauma to the pituitary stalk, interrupting the delivery of hypothalamic hormones to the anterior pituitary, causes a decrease in the secretion of all anterior pituitary hormones except prolactin, which increases.

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2.2 Adenomas

- Most common cause of anterior pituitary dysfunction.
- Microadenoma < 1.0 cm in diameter and do not have a mass effect; do not cause hypopituitarism.
- Macroadenomas > 1.0 cm in diameter and can produce a mass effect, the consequences of which correlate with size.
- Most common functional (secreting) is a prolactinoma (60%), then GH-secreting (20%) acromegaly and ACTH-secreting (10%) Cushing disease. A growth hormone-prolactin functional adenoma is not unusual.
- A common consequence is hypogonadism due to disruption of the GnRH-gonadotropin axis. Prolactin also is know to inhibit GnRH.
- Prolactinemia in women is associated with decreased libido, amenorrhea, and galactorrhea. In men, it is decreased libido and impotence.
- Prolactinemia also can occur because of pituitary stalk trauma, hypothyroidism, estrogen therapy, and oral contraceptives. If the disorder is long-lasting, the secondary effects of hypogonadism are evident, including osteopenia, reduced muscle mass, and reduced beard growth in men.
- Growth-hormone-secreting tumor usually is a macroadenoma.
- Cushing disease almost always is a microadenoma and ACTH is not elevated sufficiently to cause hyperpigmentation.

2.3 Sheehan Syndrome

- Postpartum pituitary infarction.
- During pregnancy, the pituitary enlarges in response to estrogen stimulation of the lactotrophs, but there is no compensatory increase in vascularity. Thus, following delivery, the pituitary is more susceptible to blood loss and the ensuing hypotension.
- Can result in partial or complete pituitary insufficiency.
- Often expressed as an inability to nurse and amenorrhea.

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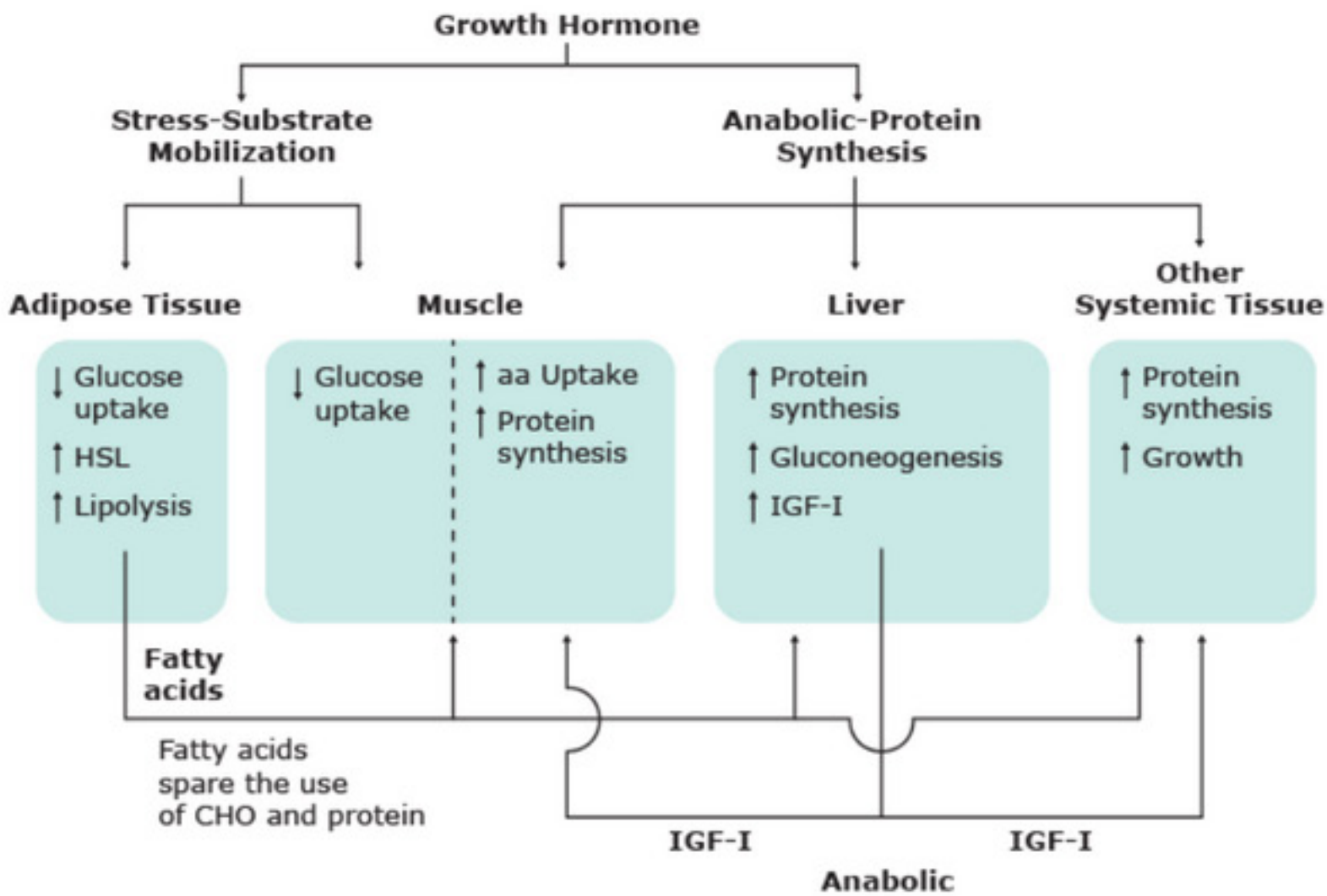
3 Growth Hormone

- Growth hormone is a peptide hormone with a structure similar to prolactin and human placental lactogen (hPL). Growth hormone can act as an agonist for the prolactin receptor.
- Much of the circulating growth hormone is bound to protein, which increases its half-life to about 20 minutes.
- Growth hormone is a substrate-mobilizing stress hormone and also is an anabolic growth-promoting hormone. The following figure tries to separate the stress versus the anabolic effects.



▲ **Figure 32–3.0** Peripheral Actions of Growth Hormone

3.1 Growth Hormone as a Stress Hormone

- Growth hormone is considered a major fat-mobilizing hormone. It increases the activity of hormone-sensitive lipase in adipose tissue, thus promoting lipolysis and a rise in circulating free fatty acids. It increases in most stresses, including exercise.
- It decreases the uptake of glucose in adipose tissue and muscle. This is considered an anti-insulin effect of growth hormone (insulin is necessary for glucose uptake in these tissues) and blood glucose rises. An excessive secretion of growth hormone promotes diabetes mellitus. There is a ketogenic effect of growth hormone because of the increased delivery of fatty acids to the liver.
- The stress effects are due to the direct effects of growth hormone on peripheral tissues. This shifts energy metabolism toward lipids and conserves carbohydrate and protein.

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3.2 Growth Hormone as an Anabolic Hormone

- Growth hormone increases the uptake of amino acids by cells, promotes protein synthesis, and decreases proteolysis.
- The increased availability of fatty acids as a source of energy is considered to *spare* the use of amino acids and direct them toward protein synthesis (promotes a positive nitrogen balance).
- Most of the anabolic actions of growth hormone are indirect via insulin-like growth factors (IGFs).

3.3 Insulin-Like Growth Factors

- Originally referred to as somatomedins because their synthesis was stimulated by growth hormone. IGF-II has important functions in the fetus and IGF-I is the main circulating form post-delivery.
- Growth hormone acting mainly on the liver stimulates the production and release of IGF-I into the circulation. Growth hormone also stimulates the production and release of IGF-binding proteins.
- IGF-I is a peptide hormone similar in structure to proinsulin but circulates strongly bound to protein. This greatly increases its half-life to about 20 hours.
- Because IGF-I is dependent on growth hormone for its synthesis and release, and because it has a long circulating half-life, the plasma level of IGF-I is usually a good index of overall growth hormone secretion.
- Growth-hormone secretion is pulsatile and most of the pulses are released during the night; as such, a single measurement of plasma growth hormone is not a good index of overall secretion.
- In some cases, control of IGF-I can be independent of growth hormone. For example, in a state of long-term stress (e.g., in starvation) growth hormone ↑ but IGF-I ↓.
- IGF-I has some intrinsic insulin activity and subcutaneous injections can cause hypoglycemia.
- IFG-I is now considered a major anabolic growth factor. It promotes protein synthesis and helps maintain a positive nitrogen balance. Decreased lean body mass with aging may be in part due to a decrease in the growth hormone IGF-I axis. The first major confirmed action of IGF-I was that it increased the synthesis of cartilage in the epiphyseal plates of long bones. It is possible that all of the actions of growth hormone on bone are via IGF-I.

3.4 Control of Growth-Hormone Secretion

- Acute factors that promote growth-hormone secretion include most stresses, hypoglycemia, and amino acids.
- Factors that suppress growth-hormone secretion include hyperglycemia and a weak negative feedback via IGF-I.
- Most (70%) of the pulsatile release of growth hormone occurs during slow-wave sleep (stages 3 and 4) and this increases during puberty. Nocturnal pulses are not suppressed by glucose.

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4 Growth and Growth Hormone

4.1 Prepuberal Growth

- All anabolic hormones (growth hormone IGF-I, thyroid hormone, insulin), except anabolic steroids, are required for normal prepuberal growth. Thyroid may also have some permissive actions. It is required for the synthesis and the secretion of growth hormone.
- A hypersecretion of growth hormone prepuberty promotes giantism (pituitary adenoma) due to an accelerated growth rate and the delay in puberty.
- Growth-hormone deficiency causes dwarfism.
- There is a dwarfism of tissue resistance to growth hormone (Laron syndrome) characterized by ↑ growth-hormone secretion but ↓ plasma IGF-I.
- Both forms of dwarfism are treatable.

4.2 Puberty

- The increased growth rate of puberty is initiated by an increase in androgen secretion. In men, it is testosterone; in women, it is adrenal androgen. ↑ Androgen drives ↑ growth hormone drives ↑ IGF-I drives long-bone growth.
- Androgens also terminate long-bone growth by causing the mineralization of the epiphyseal plates. Estrogen has a similar effect. In men, the small amount of estrogen produced from the peripheral conversion of testosterone may play a significant role in plate closure. Men with aromatase deficiency are associated with tall stature. Estrogen also is important in advancing bone age and increasing bone density.
- Peak IGF-I concentrations are achieved after peak growth and remain elevated for several years.

Note: Androgens initiate the period of rapid growth; androgens, along with estrogen, terminate that growth.

4.3 Postpuberty

- Secretion of growth hormone decreases normally with age. It is evident in the sedentary population, but can be somewhat mitigated by regular exercise.
- In the past, a deficiency in growth hormone was considered a benign problem. There were episodes of hypoglycemia but that was not treated.
- It is now recognized that growth-hormone deficiency also results in increased adipose tissue, decrease in lean body mass, and probably negative effects from lower circulating IGF-I. As such, it is now a treated condition.
- The most sensitive test for a deficiency of growth hormone is an insulin-induced hypoglycemia. The test considered safe for anyone except those with cardiovascular disease or the elderly. However, an arginine infusion test is considered the more acceptable approach.
- Growth-hormone deficiency may foreshadow the loss of other pituitary hormones.

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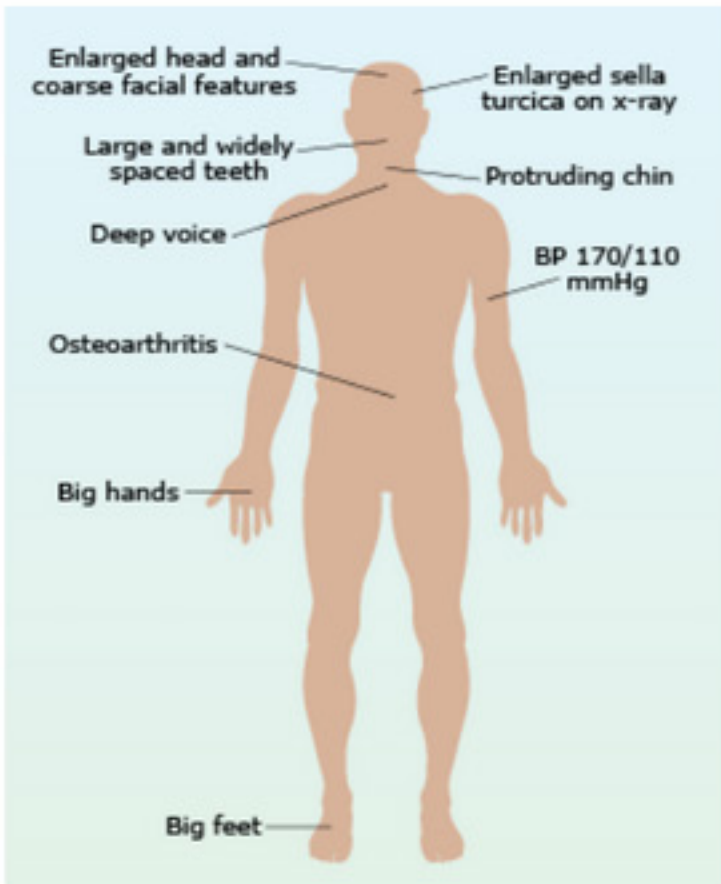
4.4 Acromegaly

- A hypersecretion of growth hormone is almost always due to a macroadenoma (> 1.0-cm diameter) of the anterior pituitary.
- The ↑ growth hormone leads to ↑ IGF-I, which causes most of the consequences of acromegaly.
- Tumor may also contain lactotrophs, and there may be a concurrent increased secretion of prolactin.
- Growth-hormone secretion remains pulsatile but nocturnal dominance is lost. Plasma levels are elevated but not diagnostic for the disorder.
- Screening is for elevated plasma IGF-I. Diagnosis is confirmed by demonstrating the failure of an oral glucose load to suppress growth hormone. Tumor usually remains responsive to somatostatin.
- Physical consequences include:
  - General local overgrowth of cartilage, bone, and soft tissue.
  - Enlargement of the skull with a downward and forward growth of the mandible (prognathism); widely separated front teeth.
  - Enlargement of the hands and feet (acral) and coarsening of facial features.
  - Question to ask: Has your shoe (or glove) size changed?
  - Headache is common but visual impairment is rare.
- Hypogonadism in part due to tumor compression and increased prolactin secretion.
- Insulin resistance and intolerance due to growth hormone and not IGF-I. Hyperglycemia can lead to type 2 diabetes.
- Accompanied by hypertension, cardiovascular disease, and visceromegaly.



▲ **Figure 32–5.0** Clinical Presentation of Acromegaly

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1 General Characteristics

- Composed of cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus.
- Posterior pituitary is not a gland per se but a collection of nerve endings (adenoma of the posterior is a distractor on the exam).
- ADH = arginine vasopressin. Both ADH and oxytocin are nanopeptides.
- Oxytocin has receptors on uterine muscle at term and is involved with milk ejection.
- Action potentials originating on the neuron cell body and terminating in the posterior pituitary represent the stimulus to release the vesicles of ADH (mechanism is similar to that described for the synaptic junction).
- ADH has a half-life of just a few minutes.

Note: ADH is a hormone that is quickly mobilized and its action is quickly terminated.

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2 Role of ADH

- ADH can be considered the main hormone regulating ECF volume. Because of its short-term rapid action, ADH is the acute regulation of ECF volume. The renin-angiotensin-aldosterone system is then the long-term regulation of ECF volume.
- ADH controls ECF osmolarity (sodium concentration). The osmoreceptors in the hypothalamus are very sensitive receptors, and osmolarity can generally be maintained within 1% to 2% of the set point for the ECF (280-285 mOsm/L).
- It could be argued that by controlling osmolarity, ADH is actually controlling volume. Acute changes in volume usually are accompanied by changes in osmolarity. Sweat and insensible water loss are all hypotonic and thus represent a loss of free water (↑ ECF osmolarity). An increase in ADH conserves free water. Thirst plays a major role in returning free water to the ECF. The most potent stimulus for thirst is a rise in the ECF osmolarity.
- Volume receptors are stretch receptors within the walls of large veins and the heart atria. Sensitivity of the receptors is such that there must be a 10% to 15% change in vascular volume to alter the afferent input signal to the central nervous system. Receptors regulate filling on the venous side of the circulation.
- In addition, it can be demonstrated that volume regulation takes priority over osmoregulation with volume depletion. A loss of body fluid with significant salt loss (e.g., diarrhea, sweating, vomiting) followed by fluid replenishment reduces ECF osmolarity. The osmostat is lowered and the body tolerates the lowered osmolarity in order to return volume toward normal. This is a major cause of hyponatremia in patients.
- The osmostat is lowered during pregnancy, in specific stages of the menstrual cycle and with volume depletion (i.e., ECF regulated at a lower osmolarity).
- Input also is received from the high-pressure stretch receptors of the carotid sinus and aortic arch. As long as blood pressure is within a normal range, they probably play only a minor role in regulating the secretion of ADH. However, with significant hypotension pressure regulation takes priority over venous volume regulation. In low-output heart failure, ADH is elevated in spite of the venous congestion.

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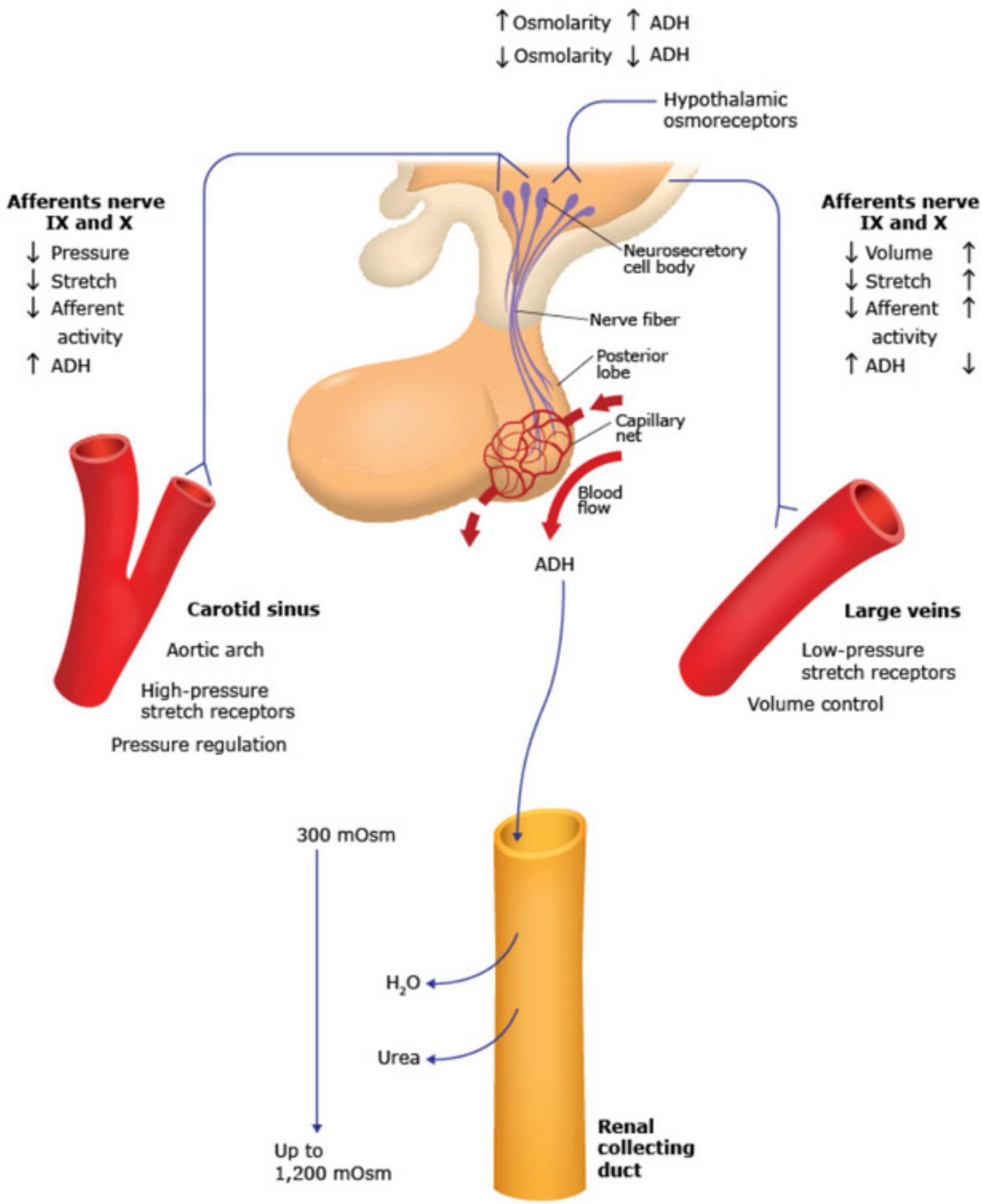

Note: Damage to cranial nerve IX or X, ↓ afferent activity, and inappropriately↑ ADH secretion (SIADH).

▲ **Figure 33–2.0** The ADH System

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3 Actions of ADH on the Kidney

- ADH increases the reabsorption of electrolytes in the thick ascending limb of the loop of Henle and the distal tubule. It also increases the reabsorption of urea from the collecting duct. These actions help maintain the high osmolarity of the medullary interstitium.
- The *main* effect of ADH is on water reabsorption in the collecting duct.
- ADH binds to V_2 (vasopression-2) receptors. The intracellular ↑ cAMP causes the insertion of aquaporin-2 (AQP2) water channels in the apical (luminal) membrane. Synthesis of the water channels also is increased. Removal of ADH removes the water channels from the membrane. Basolateral membrane has AQP3 and AQP4 channels.
- Moving water channels in and out of the apical membrane is a *fast* method of altering water reabsorption.
- Water is reabsorbed passively and drawn into the high osmolarity of the medullary interstitium. Thus, ADH has no significant effect on the metabolic rate of the kidney.
- Those who routinely take in large volumes of fluids have reduced expression of AQP2 and AQP3. They have a reduced capacity to form a concentrated urine.
- Those with restricted water intake have increased expression of AQP2 and AQP3. They have a greater capacity to form a concentrated urine.
- V_1 receptors are on vascular smooth muscle. Hypotension increases the secretion of ADH and the peripheral vasoconstriction is part of the pressure regulation role of ADH.

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4 Diabetes Insipidus

- Characteristically, the individual is forming a large volume of dilute urine (polyuria) along with polydipsia.
- If fluid intake does not match the fluid loss, the individual becomes dehydrated and hyperosmotic.
- The problem is either a deficiency of ADH (central form) or a lack of an effect of ADH on the collecting duct (nephrogenic form).

4.1 Central Diabetes Insipidus

- Deficiency of ADH; circulating levels low.
- Can be inherited but the most common cause is the result of trauma to the posterior pituitary, which may be a transient response.
- The most common tumor-derived form is a craniopharyngioma.
- Severing the posterior pituitary stalk produces a characteristic triphasic response:
  1. Diabetes insipidus.
  2. SIADH due to the uncontrolled release of ADH from the nerve terminals.
  3. Return to the symptoms of diabetes insipidus.

4.2 Nephrogenic Diabetes Insipidus

- Tissue resistance to ADH; circulating levels elevated.
- Can be inherited, acquired, or the effect of drugs (lithium).

4.3 Water Deprivation Test (Normal Plasma Osmolarity 280-285 mOsm/L)

- **Normal Individual:** The urine becomes concentrated without the plasma becoming overly concentrated (e.g., plasma = 293 mOsm/L; urine = 800 mOsm/L).
- **Diabetes Insipidus:** The plasma becomes concentrated without the urine becoming concentrated (e.g., plasma = 338 mOsm/L; urine = 101 mOsm/L).
- **Desmopressin Injection:** In the central form, the urine becomes concentrated; in the nephrogenic form, the urine remains dilute.

  Note: The quickest test to separate the central disorder from the nephrogenic disorder is to give an injection of an ADH analogue. Measuring the plasma level of ADH will also separate the two forms. Central diabetes insipidus ↓ ADH; nephrogenic diabetes insipidus ADH↑.

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5 Syndrome of Inappropriate ADH Secretion (SIADH)

- Patient appears to be well-hydrated (clinically euvolemic), but ECF hypoosmotic.
- Plasma ADH is above what would be expected on the basis of body fluid osmolarity, blood volume, and pressure.
- Causes include lesions of the baroreceptor pathway and the ectopic secretion of ADH. Small cell carcinoma of the lung secretes a number of peptides, including ADH. A small but constant secretion by a tumor may minimally affect the ability to form a dilute urine but a large acute volume load cannot be excreted short term.
- Contributing to the hypoosmotic state is the salt-wasting effect of the increased secretion of atrial natriuretic peptide and the suppression of aldosterone.
- Treatment generally is water restriction but not salt restriction.

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6 A Differential Diagnosis

- **Patient:** Dehydrated and hyperosmotic
  - Possibilities include: Simple dehydration, diabetes insipidus.
  - Separated based on a comparison of the plasma and urine osmolarities.

Dehydration: Urine osmolarity > plasma osmolarity

Diabetes insipidus: Plasma osmolarity > urine osmolarity

- **Patient:** Well-hydrated (clinically euvolemic) but hypoosmotic
  - Possibilities include: Primary polydipsia, SIADH.
  - Separated based on urine osmolarities alone.

Primary polydipsia: Minimal urine osmolarity, < 100 mOsm/L

SIADH: Urine osmolarity greater than expected, > 100 mOsm/L

- In a low-level ectopic secretion of ADH, the urine osmolarity is not higher than the plasma; it is just higher than expected for the low plasma osmolarity. In addition, an increased plasma ADH is not diagnostic for the disorder.

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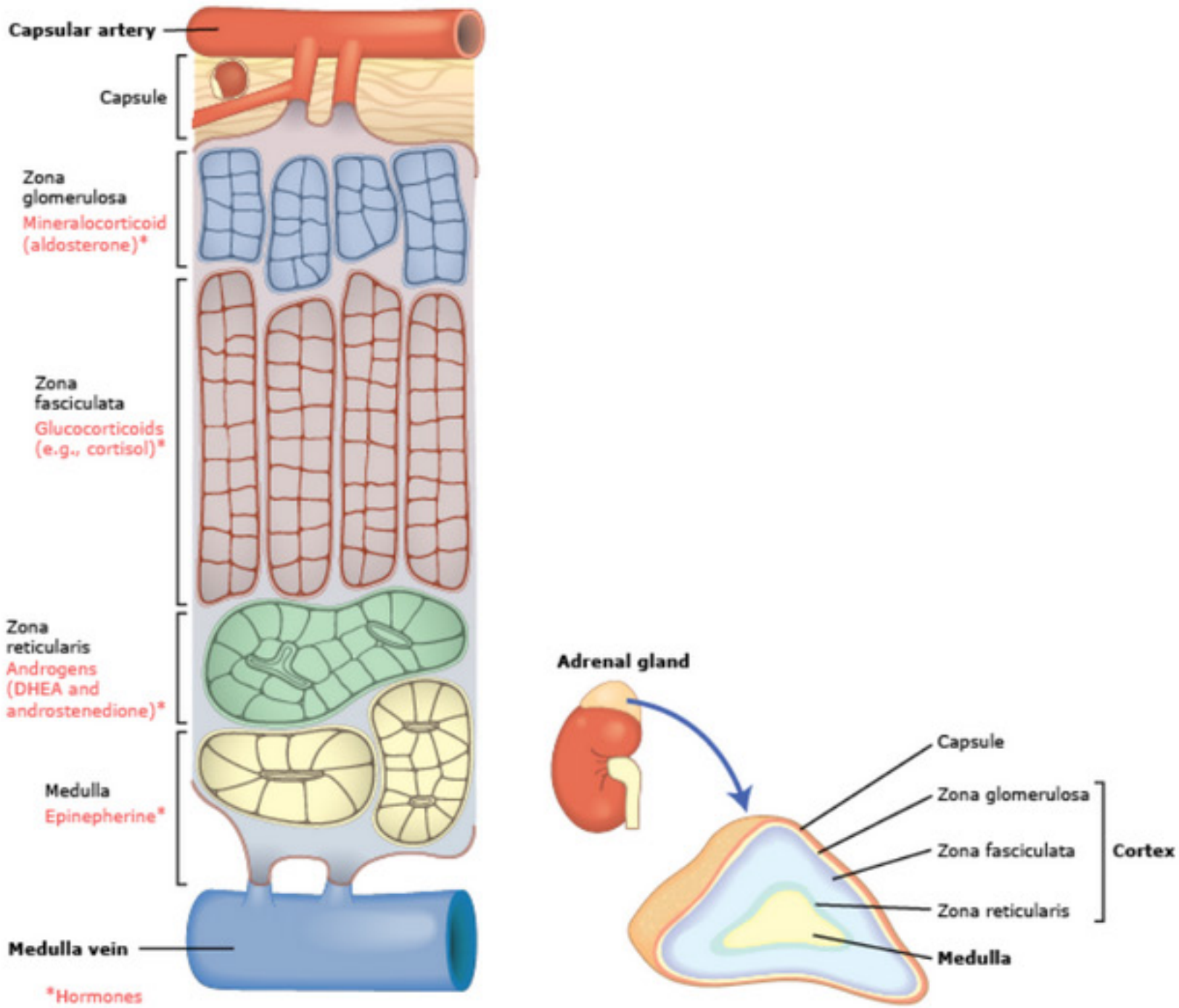
1 Adrenal Cortex



▲ **Figure 34–1.0** Adrenal Gland Regions

- **Zona Glomerulosa:** ACTH does stimulate this region but it is a transient response. The main stimulus is angiotensin II. Acting independently, an increase in K^+ (hyperkalemia) also stimulates the release of aldosterone.
- **Zona Fasciculata, Zona Reticularis:** The zona fasciculata secretes mainly cortisol and the zona reticularis secretes mainly androgens. Both regions are controlled by ACTH; as such, they should be considered a single functional zone.

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- **Medulla:** Secretes mainly epinephrine and is controlled by the sympathetic nervous system.

Note: Addison disease (primary adrenal insufficiency) represents the loss of the entire adrenal cortex. An isolated deficiency of either aldosterone or cortisol as a primary problem would be extremely rare. Single deficiencies, in most cases, represent a secondary problem.

In panhypopituitarism, cortisol is lost but the mineralocorticoid system remains intact. The loss of cortisol is the most threatening deficiency in hypopituitarism.

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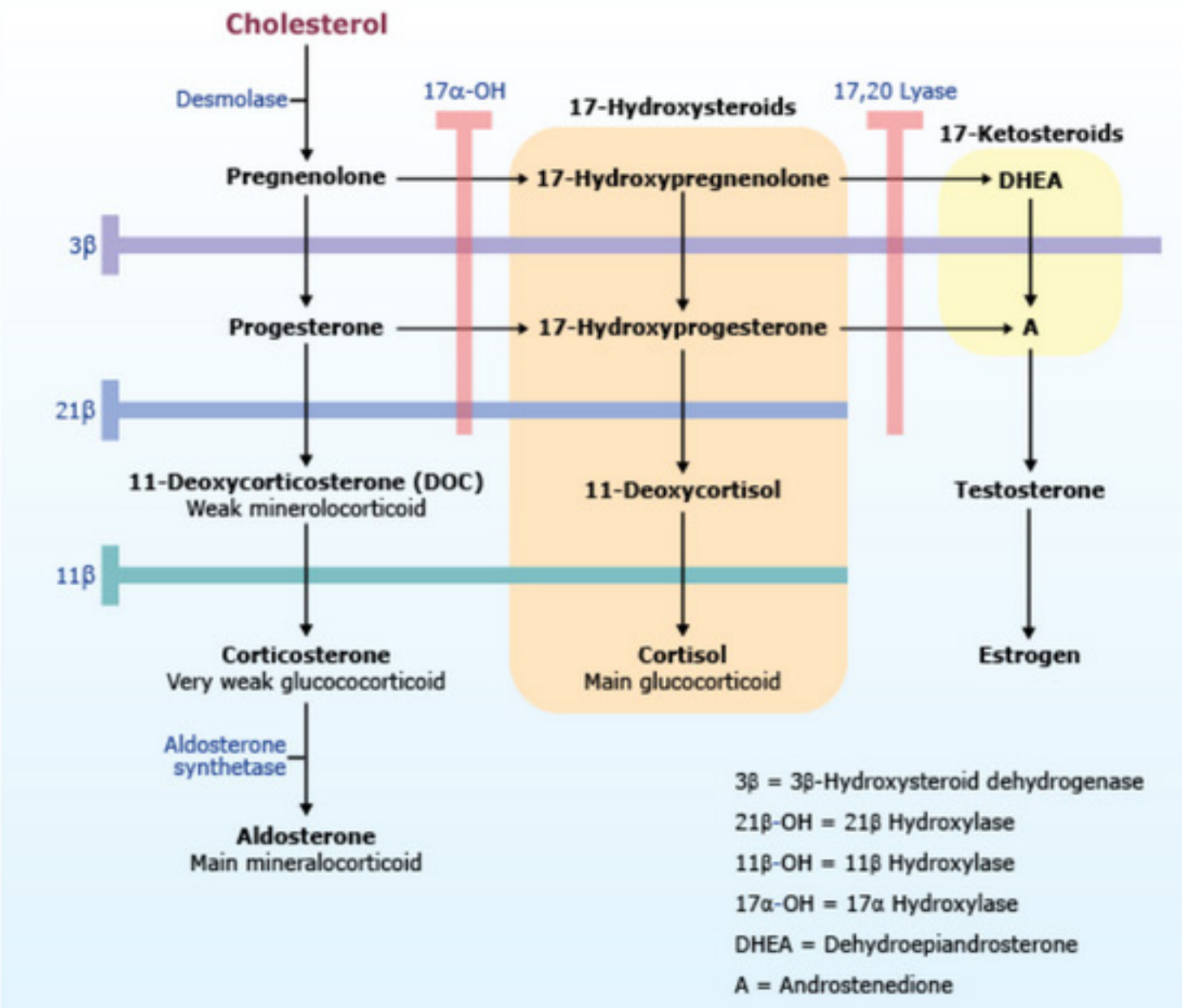
2 Pathways in the Synthesis Steroid Hormones



▲ **Figure 34–2.0** Pathways of Steroid Hormones Synthesis

- Aldosterone and cortisol have both mineralocorticoid and glucocorticoid activity. If a steroid has mainly mineralocorticoid activity, it is classified as a mineralocorticoid; if it has mainly glucocorticoid activity, it is classified as a glucocorticoid. The glucocorticoid activity of aldosterone is insignificant but high circulating levels of cortisol have significant mineralocorticoid activity. DOC is a very weak mineralocorticoid secreted by the zona fasciculata in response to ACTH. It only has significant mineralocorticoid activity at excessive levels. Corticosterone is considered to have no significant activity.
- DHEA and A are the two androgens secreted by the adrenals. The main secretion is DHEA and much of it is sulfated before release. Adrenal androgens are considered water-soluble 17-ketosteroids, are filtered by the kidney, and appear in the urine.

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- The ovaries synthesize DHEA and A as precursors to testosterone and estrogen. The ovaries do not sulfate DHEA; therefore, a rise in the circulating sulfated form indicates an adrenal, not an ovarian, origin. The ovaries also synthesize and release small amounts of testosterone.
- The Leydig cells of the testes synthesize DHEA and A as precursors for testosterone. The only significant androgen secretion of the Leydig cells is testosterone.

Note: In the adult male, the action of LH on the Leydig cells determines the circulating testosterone, and completely independent ACTH acting on the adrenal cortex determines the circulating DHEA and A.

- Testosterone is a lipid-soluble hormone and circulates bound to protein (steroid binding globulin). It is not a 17-ketosteroid, but when metabolized it is converted to a 17-ketosteroid, made water-soluble, and rereleased into the circulation. Like DHEA and A, these metabolites of testosterone are filtered and appear in the urine. In the past, urinary 17-ketosteroids were measured as an index of total androgen production.

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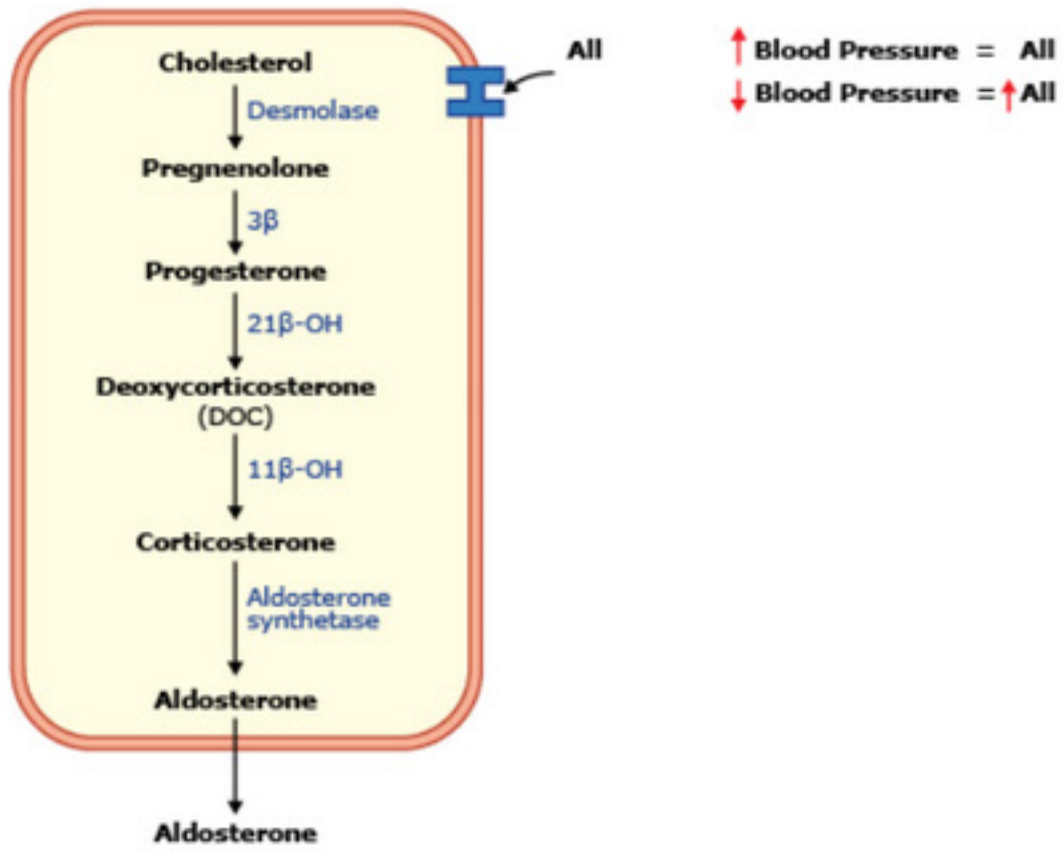
3 Steroid Hormone Synthesis in the Adrenal Cortex

3.1 Zona Glomerulosa



▲ **Figure 34–3.1** Synthesis of Aldosterone, Zona Glomerulosa

- The preceding figure shows the steroid pathway in the zona glomerulosa. All the compounds between cholesterol and aldosterone are only intermediates in this region. Three are hormones but they are not secreted. The zona glomerulosa is not the source of circulating weak mineralocorticoid (DOC). The pathway must pass through DOC to synthesize and then secrete aldosterone.
- AII is the main stimulus but acting independently, hyperkalemia also stimulates the synthesis and release of aldosterone.

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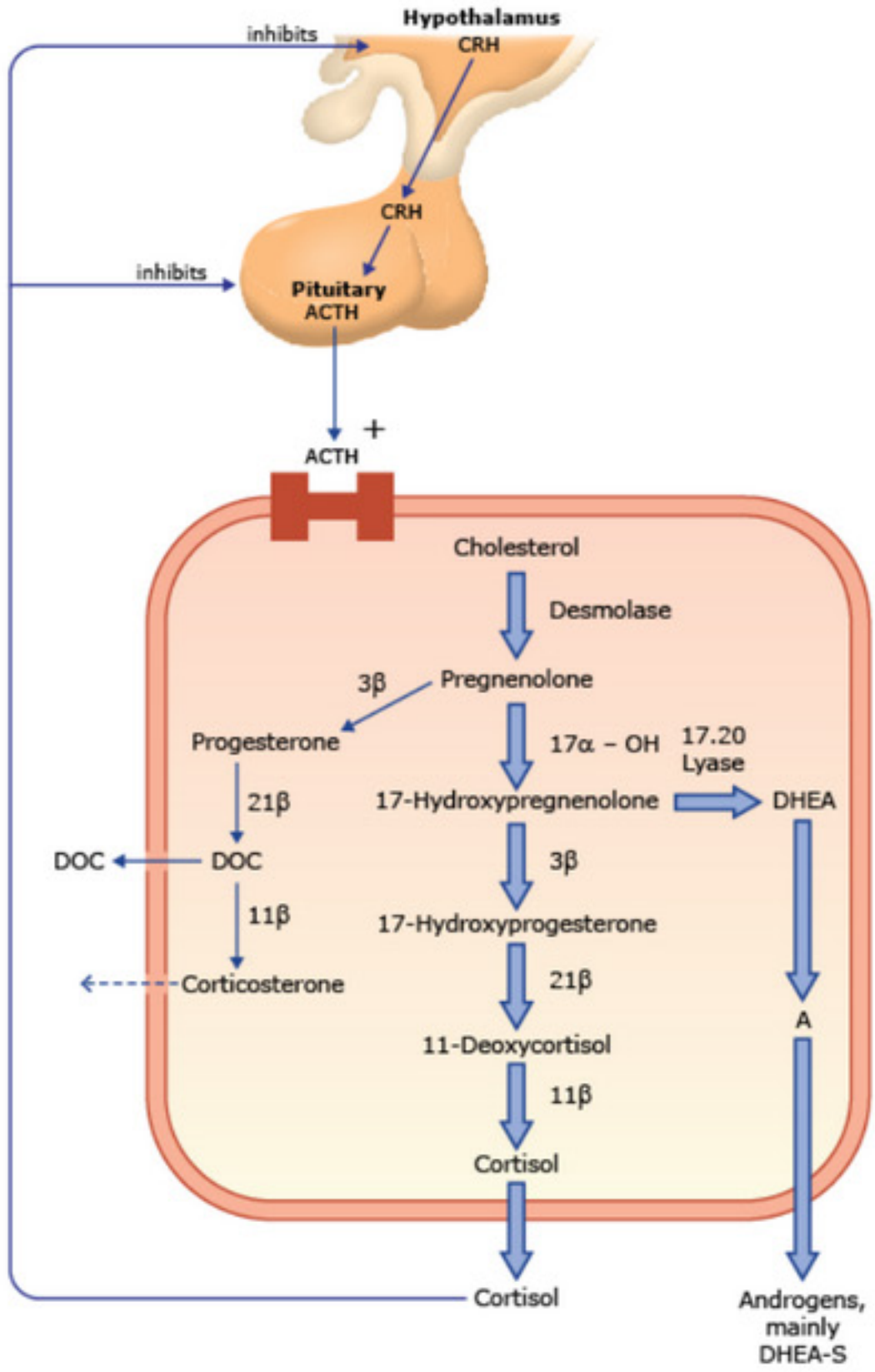
3.2 Zona Fasciculata and Zona Reticularis



▲ **Figure 34–3.2** Synthesis in Zona Fasciculata and Zona Reticularis

The preceding represent all the steroid pathways in the zona fasciculata and zona reticularis. The pathway to weak mineralocorticoid and weak glucocorticoid is only slightly expressed under normal conditions. However, a pathophysiologic acceleration of the pathway can increase the secretion of DOC sufficiently to induce hypertension. The major outputs under normal conditions include both cortisol and androgens. Negative feedback is solely via cortisol. Adrenal androgens do not feed back to inhibit ACTH. Technically, any circulating molecule with glucocorticoid activity inhibits ACTH. Feedback is proportional to potency.

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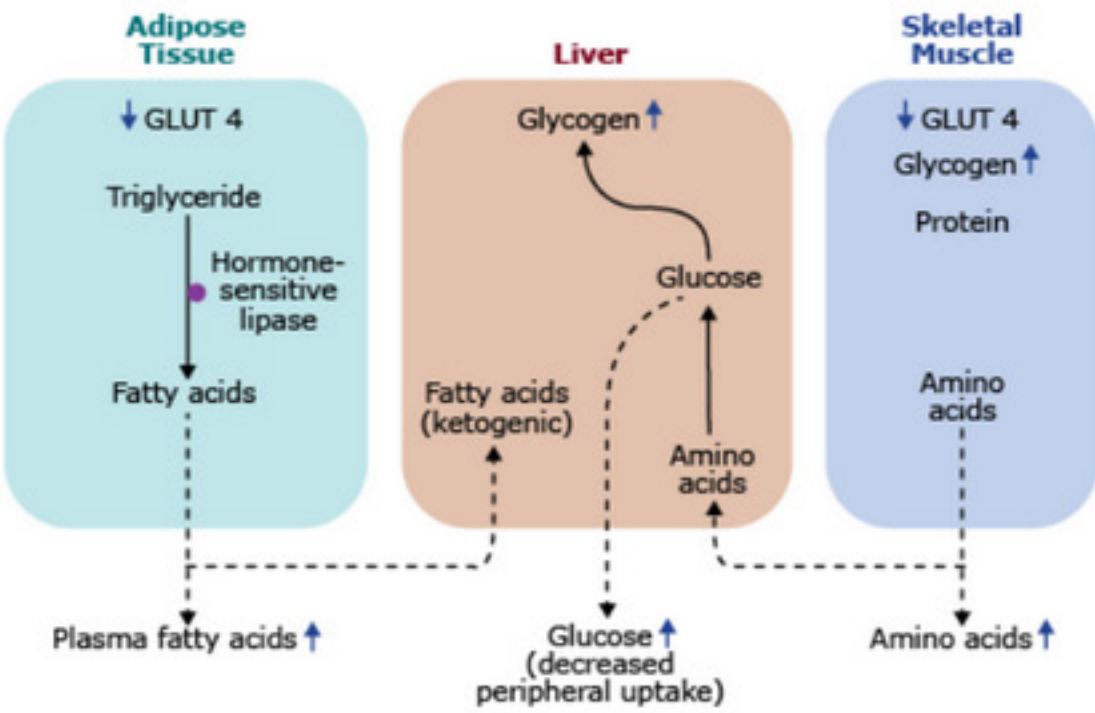
4 Physiological Stress Actions of Cortisol

- Glucocorticoids derive their name from the fact that they elevate plasma glucose.
- Cortisol circulates mainly bound to protein (corticosteroid binding globulin). The small free fraction is filtered and appears in the urine.
- The main site of inactivation of cortisol is the liver. The metabolites are conjugated to water-soluble forms which are readily excreted in the urine. Urinary 17-hydroxysteroids were once an index of cortisol secretion.

  Note:
  - Urinary 17-ketosteroids are an index of all androgen secretion.
  - Urinary 17-hydroxysteroids is an index of cortisol secretion but it includes other 17-hydroxysteroids. Urinary-free cortisol is more reliable.
- The main target tissues for cortisol's metabolic stress actions are the same as insulin: Adipose tissue, liver, and skeletal muscle. Although insulin is anabolic and increases the storage of CHO, fat, and protein, cortisol does the opposite. However, even though cortisol mobilizes and raises plasma glucose, it does not promote glycogenolysis. Instead, it accelerates gluconeogenesis.

The following is a summary of cortisol's metabolic actions:

- Protein is lost particularly from skeletal muscle. Glycogen stores, if anything, increase. Lypolysis increases fatty acids, and gluconeogenesis increase glucose output by the liver. Cortisol does inhibit the secretion of insulin. Thus, plasma insulin will be somewhat lower than expected for a given plasma glucose.
- Additional actions of cortisol include stimulating erythropoeitin synthesis, increased bone resorption by ↓ Ca^{++} absorption from the gut and reabsorption by the kidney, ↓ osteoblastic activity, and inhibiting collagen synthesis.
- Cortisol has permissive effects on glucagon and catecholamines, and inhibits ADH.
- Anti-inflammatory and immunosuppressive actions.
- It is possible but difficult to survive without cortisol even under normal living conditions and eating regular meals, but a deficiency of cortisol can be life-threatening in a stressful situation. For example, not having regular meals would result in severe hypoglycemia.



▶ **Figure 34–4.0** Metabolic Actions of Cortisol

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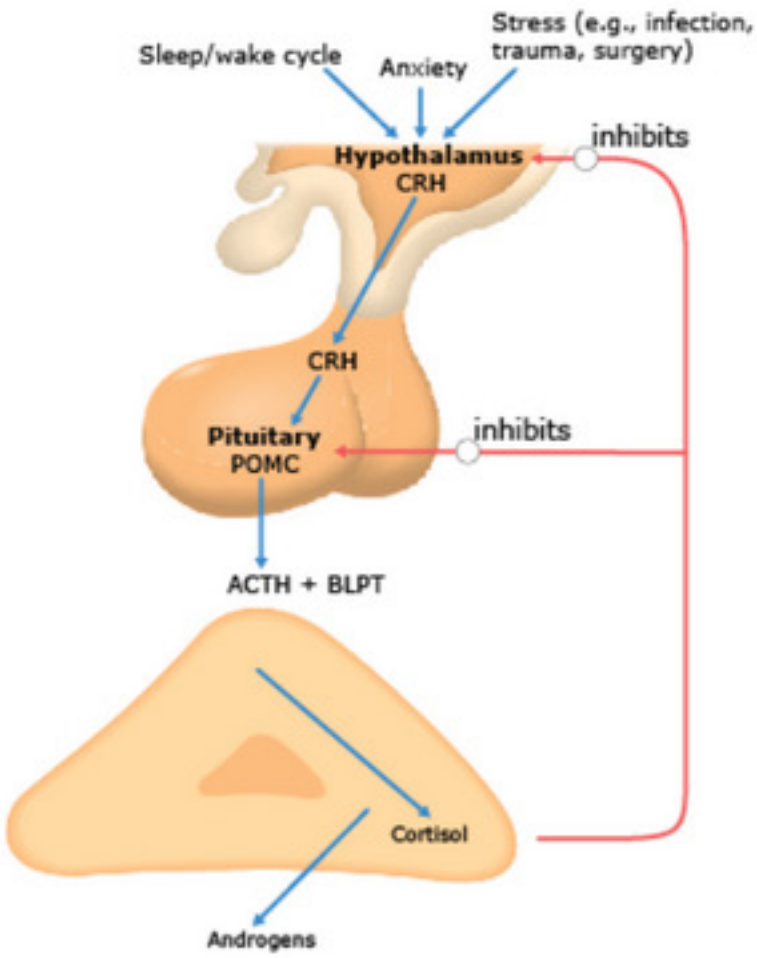
5 Control of Cortisol Secretion



▲ **Figure 34–5.0** Control of Cortisol Secretion

- In response to CRH, the corticotrophs synthesize and package the ACTH precursor proopiomelanocortin (POMC). The POMC is cleaved enzymatically before or during the secretory process.
- Equimolar concentrations of ACTH and β-lipotropin (β-LPT) are released into the circulation. β-LPT can be degraded further into β-melanocyte stimulating hormone (β-MSH) and endorphins, which may modulate the sensation of pain.
- β-MSH promotes hyperpigmentation (mucous membranes), or darkening of the skin. ACTH has the amino acid sequence for α-MSH and also promotes hyperpigmentation. This is generally expressed only with an unusually large nonphysiological secretion of ACTH, as occurs in Addison disease. Tumor secretion of ACTH is usually below the threshold for obvious hyperpigmentation.
- Cortisol, not adrenal androgens, represents the negative feedback loop. Cortisol acts at both the hypothalamus and the anterior pituitary. Feedback to the hypothalamus is particularly strong. High-dose glucocorticoids that suppress ACTH act mainly on the hypothalamus.
- There is a circadian rhythm based on the sleep-wake cycle. The highest plasma cortisol is early in the morning just before arousal. The levels slowly decrease during the day to the low point, just above zero late in the evening after going to bed. Stress-induced secretion of ACTH can eliminate the periodicity.

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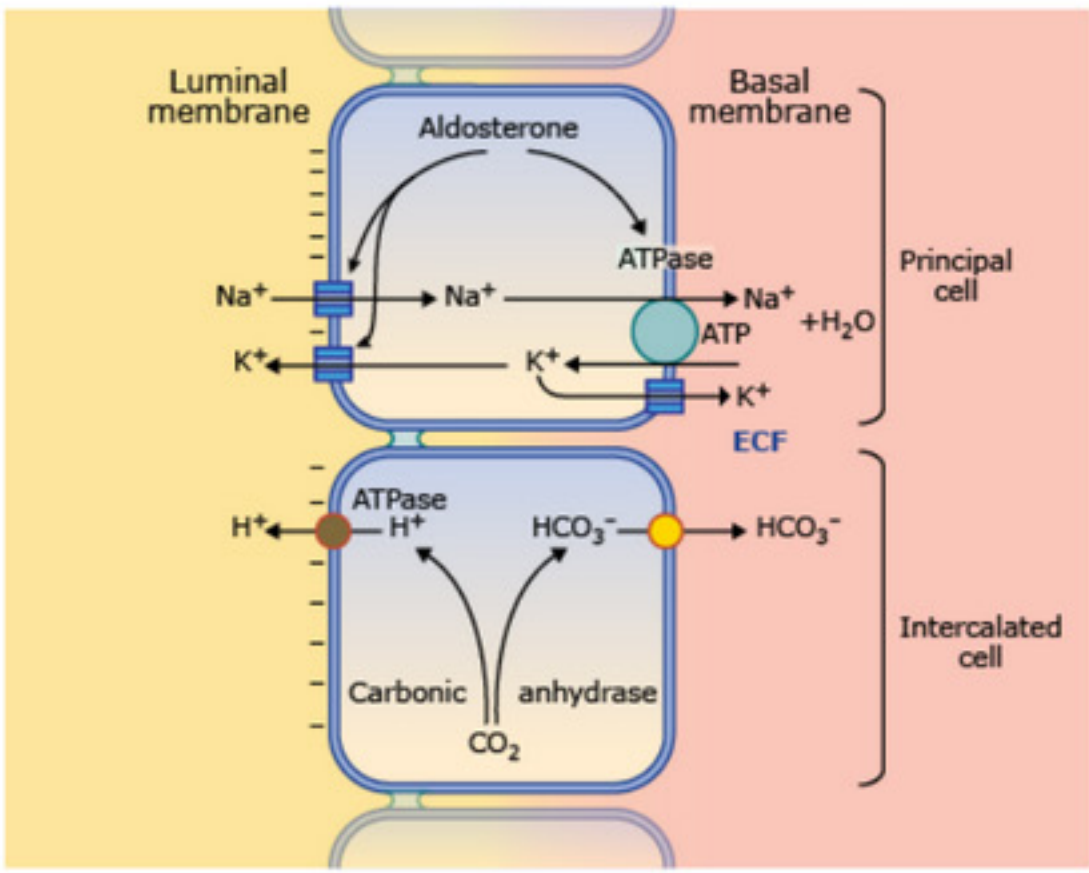
6 Physiological Role of Aldosterone

- Aldosterone's main action is to regulate ECF volume. This function is based on aldosterone's effect on the excretion of sodium by the kidney.
- Because the water follows the sodium, ECF volume is regulated. Under physiological conditions, aldosterone does not affect ECF sodium concentration.

Generalization: Aldosterone regulates whole-body sodium, whereas ADH regulates sodium concentration. In both cases, it is the ECF volume which is regulated. ADH functions rapidly (acute volume regulation) and aldosterone functions slowly (chronic volume regulation). The kidney's response to sudden changes in sodium intake takes several hours, and days are required to bring the individual back to a steady state.

- Other targets for aldosterone include salivary glands, sweat glands, and the colon. Aldosterone's effects on the colon are similar to its effects on the kidney.
- Aldosterone also regulates ECF potassium concentration.
- Aldosterone circulates weakly bound to albumin. Approximately 50% circulates free in the plasma. DOC, like cortisol, circulates tightly bound to protein. A minimum is in the free form; thus, minimal activity in the circulation. Free aldosterone appears in the urine and it is readily quantitated.

6.1 Actions of Aldosterone on the Kidney



▲ **Figure 34–6.1** Actions of Aldosterone on the Distal Tubule Collecting Duct of the Kidney

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- Aldosterone increases the activity of the Na/K-ATPase pump on the basolateral membrane where sodium is exchanged for potassium. This pump is the driving force for sodium reabsorption and potassium secretion.
- Aldosterone increases the number of open sodium channels in the luminal membrane allowing the passive entry of sodium into the tubule cell. Water follows the sodium and there is no change in the ECF sodium concentration.
- Chloride does not follow sodium proportionately across the luminal membrane. As such, the lumen of the tubule develops a negative charge. Aldosterone also increases the expression of open potassium channels in the luminal membrane. The potassium pumped into the cell from the ECF normally diffuses back through the leak channels. The negative luminal charge attracts and promotes the secretion of potassium into the tubule lumen.
- The negative luminal charge facilitates the pumping of hydrogen ions (H/K-ATPase) into the tubule lumen, and thus the excretion of acid in the urine. When hydrogen ions are lost in the urine, new bicarbonate is added to body stores.

  In summary: Aldosterone ↑ Na^+ and H_2O reabsorption, ↑ K^+ and H^+ secretion, and ↑ body HCO_3^-.
- Acting independently, potassium (hyperkalemia) stimulates the secretion of aldosterone but suppresses the renin-angiotensin system.

  Note: Aldosterone regulates whole-body sodium but regulates the ECF concentration of potassium.
- Most investigators consider ACTH to have a minor, or no, role in the regulation of aldosterone. Exogenous glucocorticoids suppress ACTH but a normal secretory response to aldosterone remains. Physiologically, they are independent systems.
- It would be virtually impossible to survive without any mineralocorticoid activity.

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7 Control of Aldosterone Secretion

Aldosterone's secretion is mainly determined by its role as part of the renin-angiotensin-aldosterone system. It is mainly a volume-regulating system and represents the chronic regulation of blood pressure. Acute regulation is the carotid sinus reflex and, in certain emergencies, ADH.

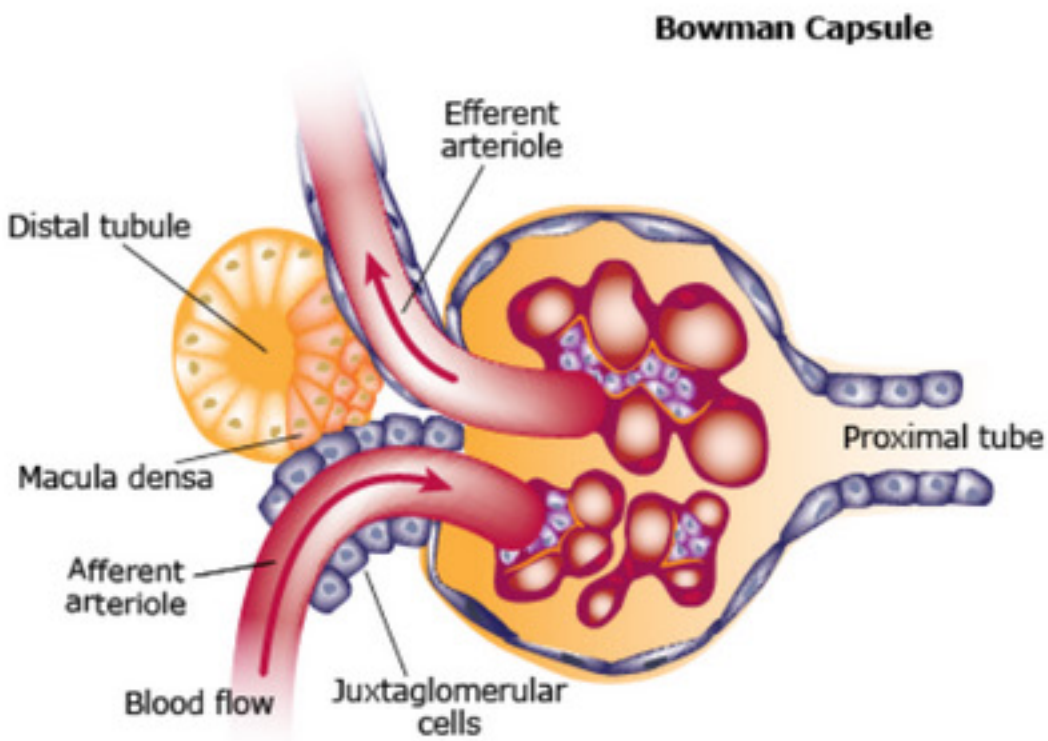
Any system that regulates blood pressure, whether acute or chronic, can be related to the following equation, as was seen earlier in the peripheral circulation:

$$MAP = CO \times TPR$$

There must be a sensor to monitor an index of blood pressure and the system must be able to manipulate CO and TPR to maintain MAP close to a set point.

7.1 Sensory Input

- The main sensory cells are the juxtaglomerular cells (JG), which are modified smooth muscle cells that surround the afferent arteriole. They can be considered miniature pressure transducers that monitor blood pressure inside the kidney, specifically, as it enters the afferent arteriole. They do not monitor renal blood flow.
- The JG cells receive input from the adjacent macula densa cells, which are chemoreceptors that monitor the delivery of sodium (or possibly sodium chloride) to the distal tubule.
- A third input is received from sympathetic neurons innervating the JG cells acting through β receptors.



▲ **Figure 34–7.1** The Juxtaglomerular Apparatus

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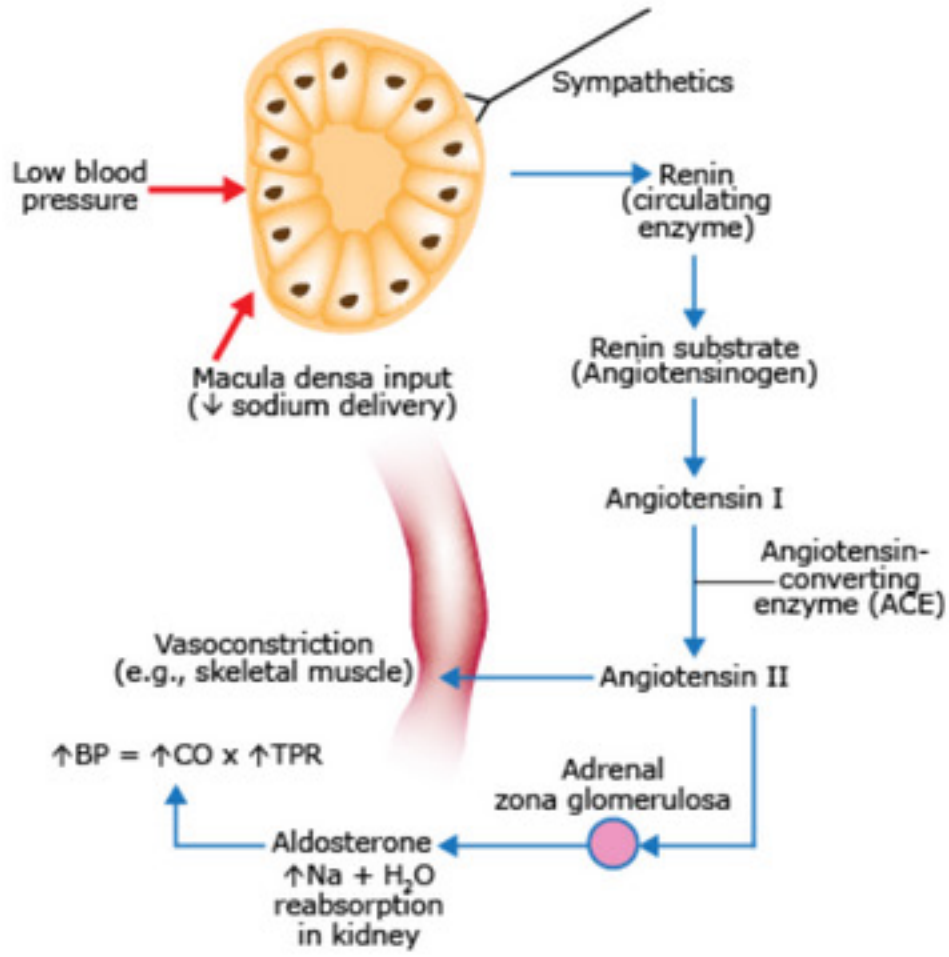
7.2 Juxtaglomerular Cell Output

- The JG cells respond to three separate inputs that increase the release of renin into the circulation:
  1. The most potent stimulus is a drop in blood pressure directly monitored by the JG cells.
  2. A decrease in the delivery of sodium to the distal tubule via the macula densa.
  3. Increase stimulation of sympathetics to the kidney.
- Renin is often referred to as a hormone, but it actually is a proteolytic enzyme. There are no renin receptors on peripheral target tissues. Renin acts on a circulating globulin referred to as angiotensinogen or renin substrate. As with other globulins, it is synthesized and released by the liver.
- Renin clips off a decapeptide from the globulin, angiotensin I (AI). AI is considered a circulating prohormone. AI is converted into the octapeptide angiotensin II (AII) by angiotensin-converting enzyme (ACE), which is present in many tissues, particularly the pulmonary vascular endothelium.
- AII is the active hormone. It has two main actions:
  1. It directly constricts the smooth muscle surrounding arterioles, particularly in skeletal muscle raising TPR.
  2. It stimulates the zona glomerulosa of the adrenals to secrete aldosterone, which increases sodium reabsorption by the kidney. Because the water follows the sodium, it increases circulating volume and, thus, cardiac output.
- AII has a half-life of about one minute. It is metabolized by angiotensinase to AIII. Although AIII has some activity it is considered a metabolic end product. Renin has a more prolonged half-life of 10 to 20 minutes.
- Other actions of AII include preferential constriction of the renal efferent arteriole to help maintain GFR as blood pressure decreases, increases sodium reabsorption in the proximal segments of the nephron, and stimulates ADH and thirst.



▶ **Figure 34–7.2** The Juxtaglomerular System

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8 Atrial Natriuretic Peptide

- A salt-wasting hormone secreted by the muscular tissue of the heart.
- It is found throughout the heart tissue but mainly in the right atrium.
- A major stimulus for its release is stretch of the atrium (volume expansion of the venous circulation).
- The main target tissue is the kidney, where it increases both sodium and water loss by the kidney (dilates the afferent and constricts the efferent arteriole).
- Its role is not well understood but overall it tends to antagonize the actions of ADH and the renin-angiotensin-aldosterone system.

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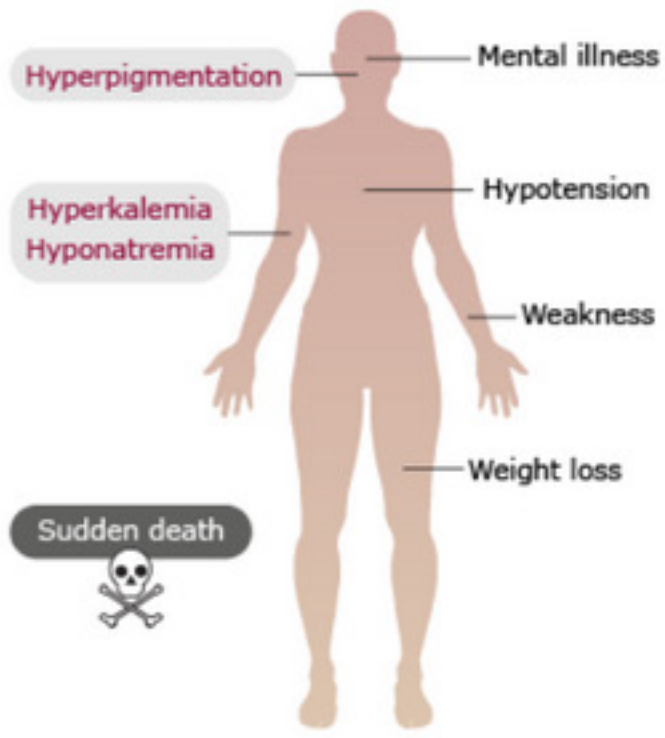
9 Pathophysiology

9.1 Primary Hypocortisolism (With Addison Disease)

- Isolated deficiency; extremely rare. It is almost always associated with Addison disease where there is a loss of the entire adrenal cortex.
- The most common cause of Addison disease is an autoimmune destruction of the adrenal cortical cells. The adrenal medulla is spared.
- With a gradual destruction of the gland, the first phase is a decrease in adrenal reserve. Adrenal crisis then appears in a stressful situation.
- Plasma values: ↓ aldosterone, ↑ renin and AII, ↓ cortisol, ↓ adrenal androgens, ↓ DOC, ↑ ACTH.
- The ↑ ACTH causes hyperpigmentation of the skin and mucous membranes. This is a classic finding and is one of the earliest manifestations of Addison disease.
- Cortisol deficiency produces fatigue, general weakness, nausea, vomiting, loss of appetite, hypoglycemia, hypotension, and hyponatremia.
- Aldosterone deficiency produces renal sodium and water loss but potassium and H^+ retention. This leads to hypotension, hyperkalemia, metabolic acidosis, and dehydration with hyponatremia.



▲ **Figure 34–9.1** Addison Disease

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9.2 Secondary Hypocortisolism

- Usually not an isolated disorder. Can be associated with pituitary tumors causing varying degrees of hypopituitarism.
- Plasma levels: ↓ ACTH, ↓ cortisol, ↓ adrenal androgens, ↓ DOC.
- Patients have the consequences of cortisol deficiency listed for Addison disease. The main difference is the lack of hyperpigmentation (↓ ACTH). Volume depletion, hyperkalemia, and severe hypotension are absent (mineralocorticoid system remains intact).
- The decreased stimulus to the adrenals results in atrophy of the zona fasciculata and zona reticularis. Reversing the atrophy is a gradual process.
- The main cause of secondary hypocortisolism is exogenous glucocorticoid therapy suppressing ACTH.
- Plasma cortisol (glucocorticoid) is elevated but ACTH, adrenal androgens, and DOC are decreased. The lack of ACTH also results in adrenal atrophy.
- Sudden withdrawal of glucocorticoid treatment can cause severe hypocortisolism. There is a time-dependent recovery of the pituitary secretion of ACTH then a further period for the adrenal to recover. Complete recovery may take up to a year. To prevent hypocortisolism, glucocorticoid treatment should be withdrawn gradually.
- Screening for hypocortisolism includes 24-hour urine cortisol or the rapid ACTH stimulation test. In the latter case, there is an increase in cortisol with a normal axis but no increase with hypocortisolism, either primary or secondary (due to atrophy of adrenals).

9.3 Cushing Syndrome

- Chronic glucocorticoid excess, regardless of the origin, leading to specific symptoms and features. Most include exogenously administered glucocorticoids but some exclude it.
- Cushing disease: Due to an adenoma of the anterior pituitary secreting ACTH (potentially suppressible).
- Ectopic ACTH syndrome: Consequences of a non-pituitary secretion of ACTH or CRH (not suppressible).

9.4 Primary Hypercortisolism (ACTH Independent)

- The most common cause is a benign adenoma of one of the adrenals secreting cortisol.
- Plasma levels: ↑ cortisol, ↓ ACTH, ↓ adrenal androgens (DHEA-sulfate), ↓ DOC, ↓ size of the contralateral adrenal.
- The tumor secretion of cortisol blunts the normal circadian rhythm.
- Removal of the tumor can cause hypocortisolism.
- In some cases, only a small amount of cortisol is secreted and these patients are described with a subclinical Cushing syndrome. A 24-hour urine cortisol test may not be sensitive enough to diagnose the disorder. A low-dose dexamethasone suppression test is then required for diagnosis.

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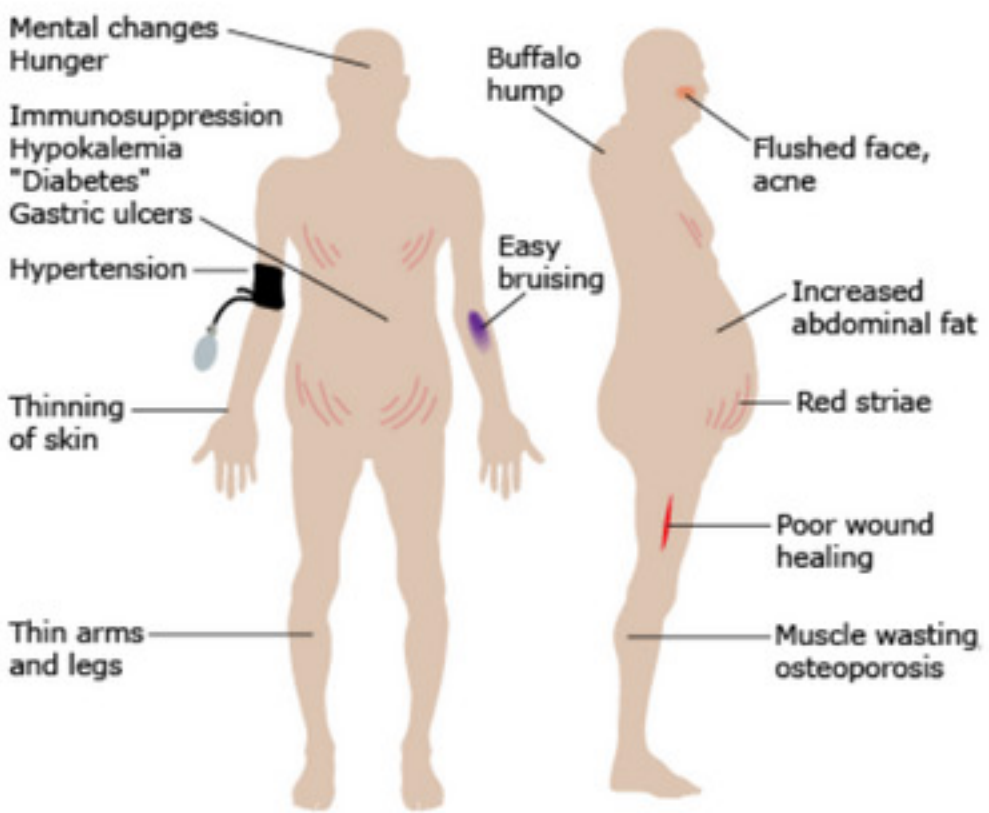
9.5 Secondary Hypercortisolism (ACTH Dependent)

- The most common cause (80% to 90%) is a microadenoma of the anterior pituitary secreting ACTH (Cushing disease). The increase in ACTH usually is not sufficient to cause hyperpigmentation.
- Ectopic ACTH secretion accounts for about 10% of the cases. This disorder may result in severe hypercortisolism, but the patients may lack the typical features of excess glucocorticoids. Bronchial and small cell lung carcinoma are responsible for about half the cases.
- Plasma levels: ↑ ACTH, driving ↑ cortisol, ↑ adrenal androgens, ↑ DOC, increased size of the adrenals (hyperplasia).
- The high-dose dexamethasone test is no longer recommended to separate Cushing disease from ectopic ACTH syndrome.

9.6 Clinical Features of Cushing Syndrome

- **Obesity:** Classically central, sparing the extremities. Fat deposits in the face create the typical *moon face,* and fat in the lower neck creates a *buffalo hump*.
- **Cutaneous:** Thinning of the skin; purple striae, which are most common in the abdomen.
- **Hirsutism:** Present in women as a result of the elevated adrenal androgens (not in primary hypercortisolism). Facial hirsutism is most common.
- **Hypertension:** Mineralocorticoid effect of glucocorticoids and in ACTH dependent increased weak mineralocorticoid.
- **Hypogonadism:** Due to elevated androgens in women and elevated cortisol in men and women.
- **Muscle Weakness:** Excessive proteolysis of glucocorticoids.
- **Osteoporosis:** Osteopenia, which often leads to osteoporosis due to the effects of glucocorticoids on bone.
- **Thirst and Polyuria:** In most cases, due to glucocorticoid suppression of ADH and the direct increase in free water clearance by cortisol.
- Inhibition of inflammatory response.
- Hyperinsulinemia and a decreased glucose tolerance due to hyperglycemia.

  Note: The insulin effect counteracts the lipolytic effect of cortisol.
- Increased appetite.
- Depression and emotional disorders.



▲ **Figure 34–9.6** Cushing Symptoms

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9.7 Primary Hyperaldosteronism (Conn Syndrome)

- Most cases involve an aldosterone-producing unilateral adrenal adenoma. Second is a bilateral hyperplasia.
- Plasma: ↑ aldosterone, ↓ K^+, metabolic alkalosis (↑ pH, ↑ $HCO3^-$). Na^+ in the upper range of normal, hypernatremia unusual.
- Increased total body Na^+ and circulating volume.
- Hypertension can be modest to severe (↓ renin, ↓ AII). A contributing factor is a peripheral vasoconstriction and ↑ TPR.
- Edema is absent due to the *escape* phenomenon. In hyperaldosteronism with hypertension, sodium and water are initially retained. At some point, the renal tubules escape from the sodium-retaining action of aldosterone and natriuresis and diuresis ensues. Atrial natriuratic hormone may play a role. There is no escape from the potassium-losing effect of mineralocorticoids.
- Patients may complain of tiredness, weakness, loss of stamina, and nocturia, all due to a loss of potassium.
- Left ventricular hypertrophy is greater than expected for the level of hypertension. Remodeling aspects of aldosterone may be responsible.

9.8 Secondary Hyperaldosteronism With Hypertension

- Renal arterial stenosis with a decrease in renal perfusion pressure is the main cause.
- Renin-secreting tumor is extremely rare.
- Consequences similar to Conn syndrome. The main difference is that with Conn syndrome there is a decrease in renin and AII, but in renal arterial stenosis there is an increase in renin and AII. It is the increase in AII that is driving the secondary increase in aldosterone.

9.9 Hyperaldosteronism With Hypotension

- Any change in blood pressure will affect the activity of the renin-angiotensin-aldosterone system. An increase in blood pressure suppresses the system promoting diuresis and natriuresis to bring blood pressure back toward normal. The reverse is also true. A decrease in blood pressure should activate the system. If this persists chronically, it would drive a secondary hyperaldosteronism.
- States in which fluid is retained but the circulating volume is below normal represent the classic example of a secondary hyperaldosteronism with hypotension. The most common example is low-output heart failure. Other examples could be cirrhosis with peripheral edema, or a stenosis of a major vein.
- Plasma: ↑ renin, ↑ AII driving the secondary hyperaldosteronism. In many cases, such as heart failure, the sodium and volume retained remains on the venous side of the circulation and cardiac output and blood pressure do not come back to normal. In hypotension, there is no sodium escape. The individual keeps retaining sodium and water until blood pressure comes back to normal. No escape means peripheral edema. *Note*: As previously mentioned, even though there is fluid retention, ADH is elevated due to the hypotension.

The presentation of hypertension with hypokalemia without the patient being on diuretics indicates a primary or secondary increase in aldosterone as the cause. If primary ↓ renin and AII, if secondary ↑ renin and AII. The preceding are classic presentations. In many cases, plasma potassium remains within the normal range.

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9.10 Pathophysiology of Sodium Dynamics

9.10.1 Sodium Regulation

- Sodium concentration regulated by ADH.
- Whole-body sodium by aldosterone (water follows the sodium).
- Aldosterone ↑ or ↓ generally does not affect sodium concentration.
- Conn syndrome (↑ aldosterone) initially does not cause hypernatremia.

Generalization: Whole-body sodium affects blood pressure; sodium concentration affects cell size.

9.10.2 Hyponatremia

- Cell swelling.
- Body fluid loss, which always includes salt wasting, plus tap water replacement is a major cause. Examples: Sweating, diarrhea, diuretics, Addison disease.
- Excess fluid intake.
- SIADH (↑ ADH).
- Patient becomes confused and disoriented.
- Most common electrolyte disorder in hospitalized patients.

Acute severe hyponatremia can result in cerebral edema with herniation of the brain stem. Requires aggressive treatment (e.g., saline and diuretics).

Chronic hyponatremia that develops more slowly is better tolerated. There is compensation by a decrease in ICF osmolarity. Aggressive treatment can cause demyelination of CNS neurons (central pontine myelinosis).

9.10.3 Hypernatremia

- Cell shrinkage.
- Usually caused by hypotonic fluid loss; hypernatremic dehydration.
- Diabetes insipidus, diuretics.
- Patient can be confused and disoriented.
- Less common than hyponatremia; osmoreceptors respond by ↑ thirst.
- Chronic compensation by ↑ in ICF osmolarity.
- Treatment is to slowly return sodium concentration toward normal; hypotonic saline, D5W.

9.11 Congenital Adrenal Hyperplasia

This represents a group of autosomal recessive disorders of the adrenal cortex where, in the most common forms, the pathway of steroid hormone production shifts from corticosteroid hormone production to adrenal androgens. Prenatal consequences in the female fetus leads to ambiguous genitalia at birth. Newborn males have normal genitalia. Postnatal consequences include masculinization in girls. The precious pseudopuberty in boys will accelerate growth rate, but the premature closure of the epiphyseal plates results in short statute.

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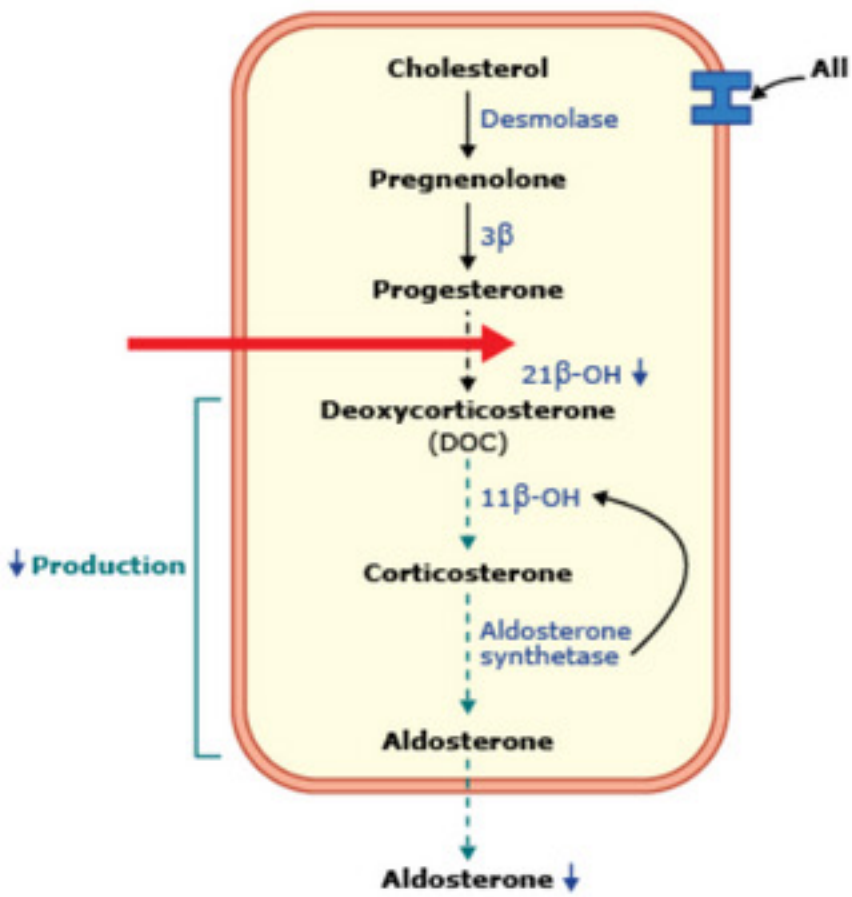
Each of the defects will have different biochemical and clinical consequences, but in all cases, there is a decrease in cortisol secretion. The result is a compensatory hypersecretion of ACTH and a hyperplasia of the adrenal cortex. There generally is only a partial deficiency. With a complete deficiency, the fetus probably would not survive. Depending on the degree of the deficiency, the individual may or may not show the classical symptoms of the disorder.

Most common are the 21β-hydroxylase (90% of the cases) and 11β-hydroxylase deficiencies. One should also consider the very rare 17α-hydroxylase deficiency. In each case, the break in the pathway undersynthesizes products beyond the break and overproduces intermediates, and shifts the pathway before the pathway break.

9.11.1 21β-Hydroxylase Deficiency

This deficiency affects the entire adrenal cortex: the zona glomerulosa, the zona fascicluata, and the zona reticularis.



▲ **Figure 34–9.11A** 21β-Hydroxylase Deficiency—Zona Glomerulosa

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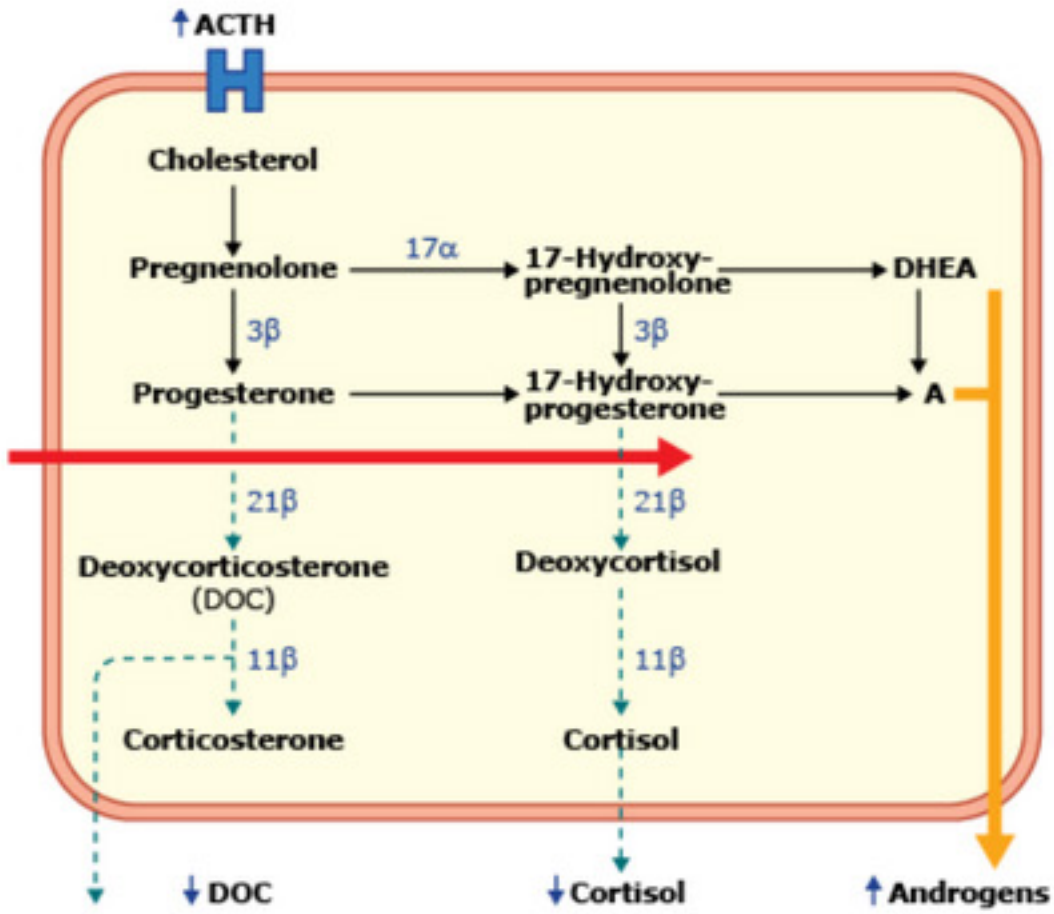

▲ **Figure 34–9.11B** 21β-Hydroxylase Deficiency—Zona Fasciculata, Zona Reticularis

Summary

- Zona glomerulosa: ↓ aldosterone
- Zona fasciculata, zona reticularis: ↓ cortisol
  ↓ DOC
  ↑ androgens
- The mineralocorticoid deficiency (aldosterone + DOC) can result in significant salt wasting and a ↓ ECF volume with hypotension. The decreased blood pressure causes ↑ renin, ↑ AII.
- The cortisol deficiency ↑ ACTH, which drives an overproduction in intermediates before the break. This would include 17-hydroxyprogesterone, a marker for the disorder. This accelerates the pathways toward the overproduction of adrenal androgens.
- Postdelivery, there are two main presentations. First, if there is significant salt wasting, the neonates have severe cortisol and aldosterone deficiencies, which will lead to an adrenal crisis. Second, the individual will have sufficient cortisol and aldosterone to prevent an adrenal crisis but maintain the virilization consequences of the elevated adrenal androgens.

Note: The exam probably will present an example of an individual with a significant non-life-threatening salt wasting that would be sufficient to cause hypotension.

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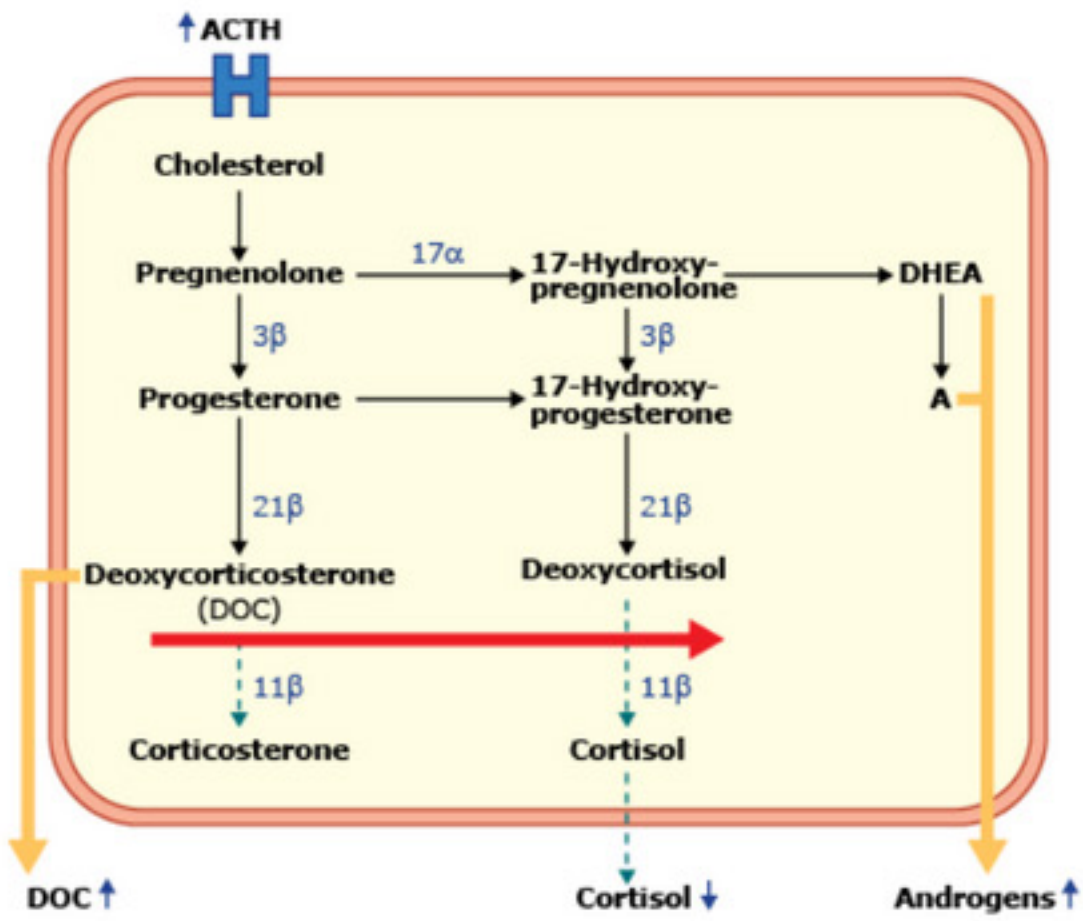
9.11.2 11β-Hydroxylase Deficiency

This deficiency only directly affects the zona fasciculata and zona reticularis . In the zona glomerulosa, aldosterone synthatase that catalyses the last two steps in the aldosterone pathway has 11β-hydroxylase activity. It is expressed by a separate gene.



▲ **Figure 34–9.11C** 11β-Hydroxylase Deficiency—Zona Fasciculata, Zona Reticularis

Summary

- Zona fasciculata, zona reticularis: ↓ cortisol
  ↑ androgens
  ↑ DOC- salt and water retention, ↑ BP
- Zona glomerulosa: The ↑ BP: ↓ renin, ↓ AII, ↓ aldosterone.

Note: ACTH drives the increase in DOC from the zona fasciculata and zona reticularis, and drives any hypertension. This would be maintained despite any decrease in aldosterone secretion.

- The individual may have hypertension associated with hypokalemia.

Important Concept

21β deficiency is a salt-wasting disorder, but the 11β deficiency is a salt-retaining disorder.

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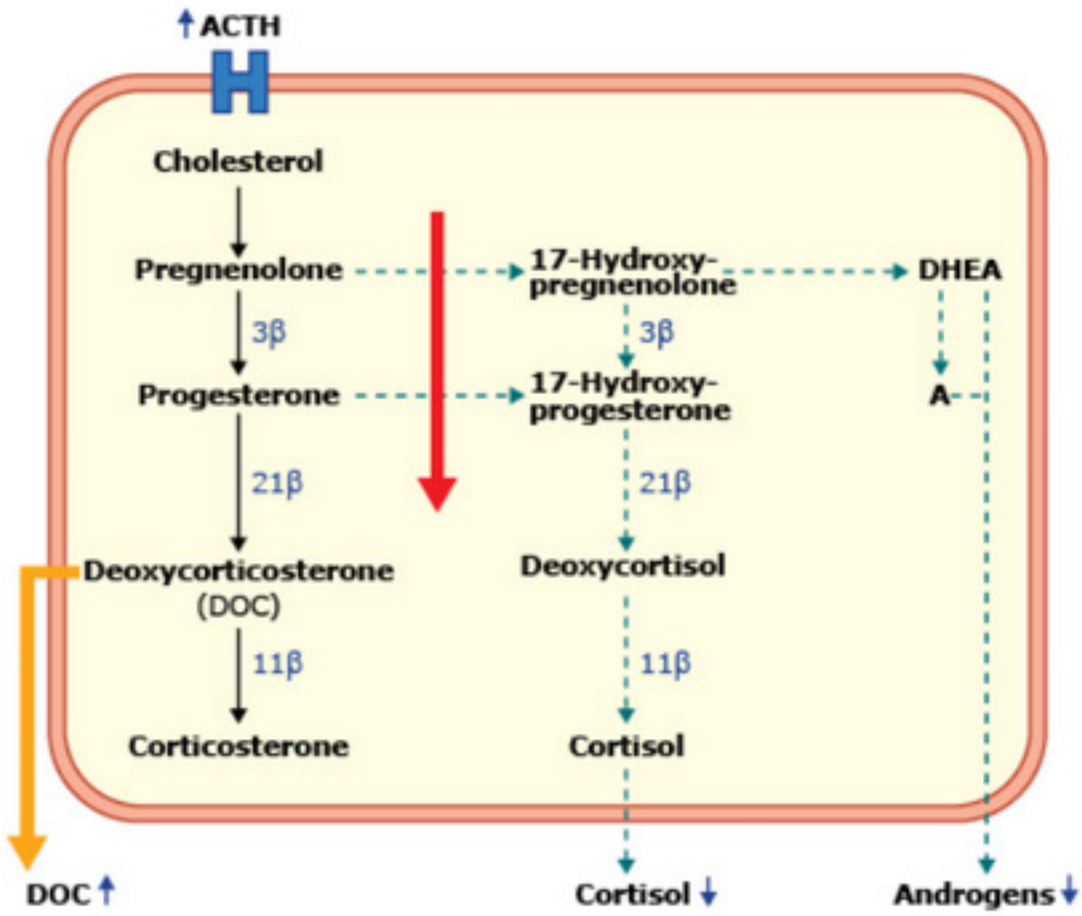
9.11.3 17α-Hydroxylase Deficiency

Deficiency affects the adrenals (zona fasciculata, zona reticularis) and gonadal sex steroids (testis and ovaries).



▲ **Figure 34–9.11D** 17α-Hydroxylase Deficiency—Zona Fasciculata, Zona Reticularis

Summary

- Zona fasciculata, zona reticularis: ↓ cortisol
  ↓ androgens
  ↑ DOC salt and water retention
- Zona glomerulosa: The ↑ BP: ↓ renin, ↓ AII, ↓ aldosterone.

Note: ACTH drives the increase in DOC from the zona fasciculata and zone reticularis, and drives any hypertension. This would be maintained despite any decrease in aldosterone secretion.

- These individuals may have hypertension associated with hypokalemia.
- The consequences in the adrenal are the same as in 11β deficiency except, in this case, there is a decrease in adrenal androgen.
- In the male fetus, the decreased androgen production can result in female genitalia.

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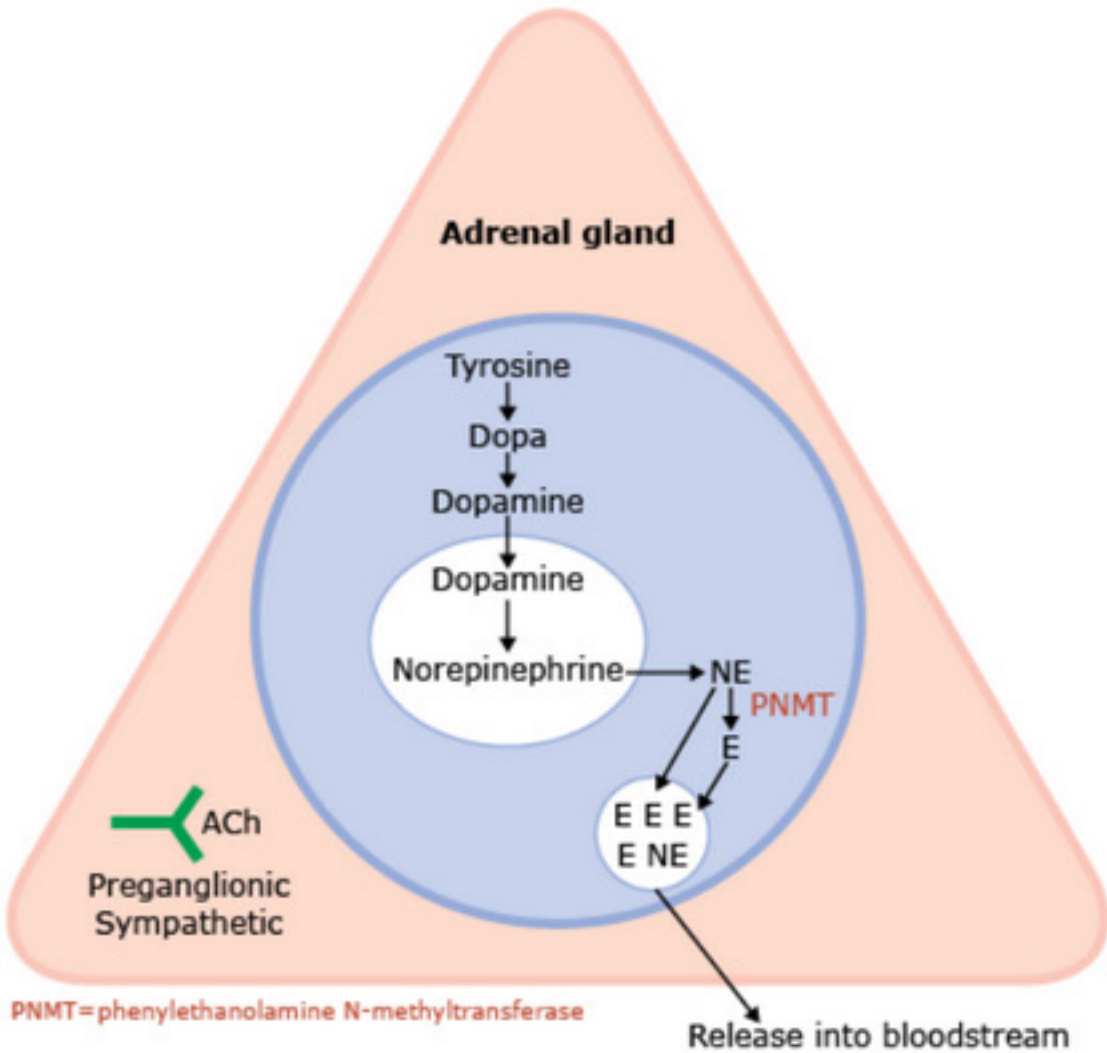
10 Adrenal Medulla

- Adrenal medulla is derived from chromaffin tissue that potentially can develop into postganglionic sympathetic neurons.
- Innervated by preganglionic sympathetic neurons releasing acetylcholine and acting on nicotinic receptors. Half-life of circulating catecholamines is only about two minutes. Adrenomedullary responses are very rapid and rapidly terminated.
- Synthesis involves the transport of tyrosine into the chromaffin cell and conversions as shown in the accompanying figure.



▲ **Figure 34–10.0A** The Adrenal Medulla

- Adrenal gland secretes 80% epinephrine (adrenalin) and 20% norepinephrine (noradrenalin).
- PNMT catalyzes the conversion of norepinephrine to epinephrine. Enzyme activity depends on the presence of cortisol from the adrenal cortex. In the absence of cortisol, the adrenal medulla secretes norepinephrine.
- Degradation involves two enzymes: Monoamine oxidase (MAO) and catecholomethyltransferase. Metabolic end products include vanillylmandelic acid (VMA) and metanephrine, which can be easily measured in the plasma and urine.

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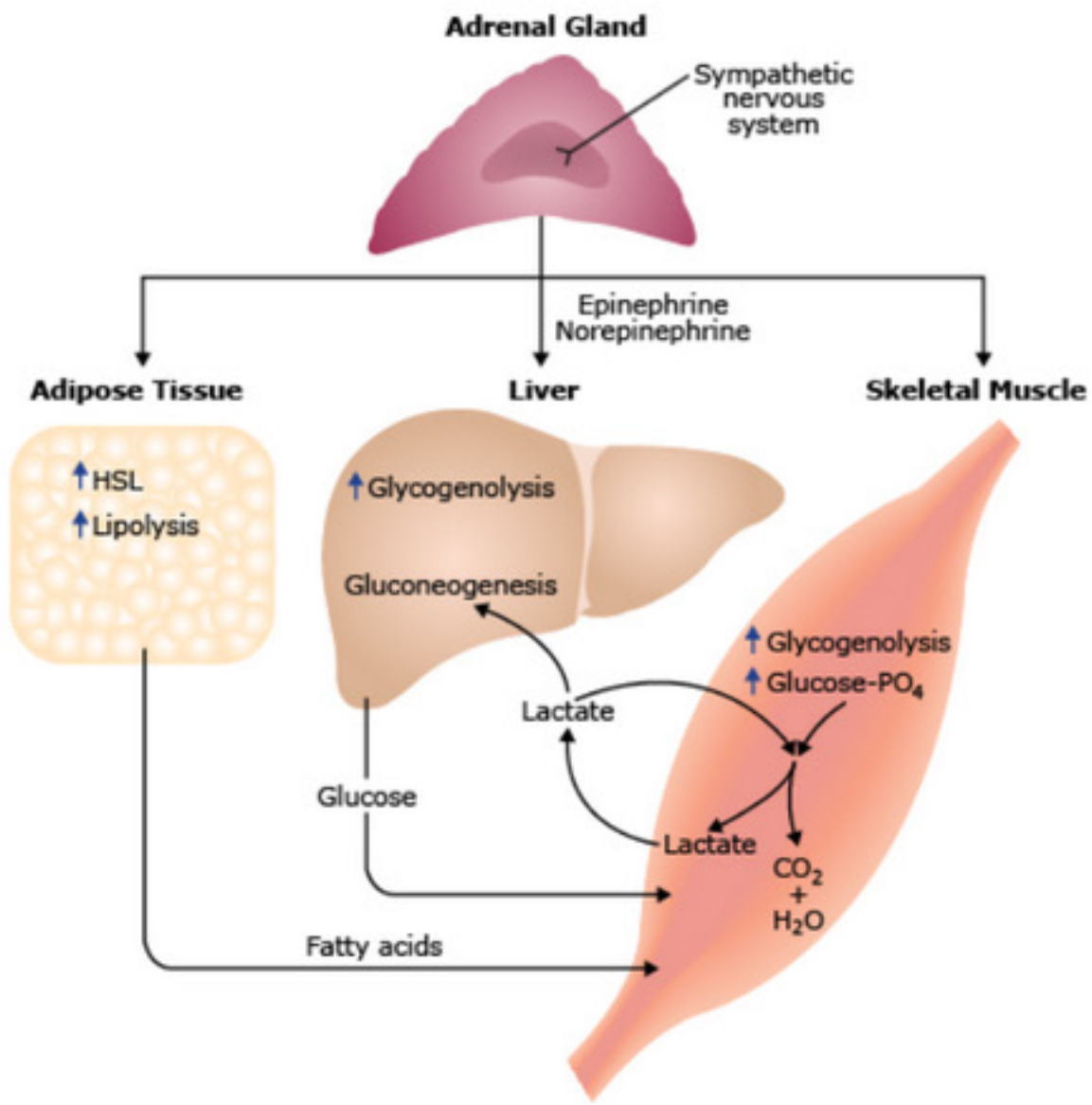
- Plasma norepinephrine originates mainly from sympathetic postganglionic neurons and plasma epinephrine from the adrenal medulla. Thus, going from a supine to a standing position will, via the carotid sinus reflex, increase sympathetic neuronal activity and plasma norepinephrine. Likewise, loss of adrenal medullary function decreases plasma epinephrine but does not significantly decrease plasma norephinephrine.
- The adrenal medulla is not required for survival because the actions of epinephrine are duplicated by norepinephrine.
- Epinephrine is one of the stress counterregulatory hormones. It is released in response to exercise, hypoglycemia, hypovolumia, exposure to cold, and other emergencies. The goal of the system is to supply the increased energy demands of heart and skeletal muscle in situations like exercise but, at the same time, to maintain an adequate glucose supply to the brain. The overall metabolic actions of epinephrine are summarized in the following figure.



▲ **Figure 34–10.0B** Metabolic Actions of Epinephrine and Norepinephrine

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There are three target tissues for the metabolic action of catecholamines:

1. **Adipose Tissue:** Increases the activity of hormone sensitive lipase (HSL), which increases triglyceride breakdown and the release of fatty acids.
2. **Liver:** Increases glycogenolysis and the release of glucose.
3. **Skeletal Muscle:** Increases glycogenolysis and the glucose-PO_4 is either fully metabolized to CO_2 and H_2O or released as lactate. Plasma lactate is taken up by the liver to be resynthetized into glucose and glycogen, or extracted by other tissues, mainly skeletal muscle and metabolized to CO_2 and H_2O.

Summary: Catecholamines mobilize carbohydrate and fat but do not mobilize protein.

10.1 Pheochromocytomas

- Pheochromocytomas and paragangliomas are catecholamine-producing tumors of adrenal or extra-adrenal origin. Paragangliomas are extra-adrenal but some restrict the term to tumors of the head and neck.
- Adrenal tumors secrete various ratios of epinephrine versus norepinephrine but usually secrete more norepinephrine. Extra-adrenal tumors rarely secrete epinephrine because they are not exposed to the cortisol necessary to facilitate the conversion of norepinephrine to epinephrine.
- Hypertension is greater with norepinephrine than with epinephrine. The dominant sign is hypertension; classically episodic but sustained hypertension is also seen.
- Tumors are encapsulated; hypertensive crisis is triggered by spontaneous hemorrhages or pressure on the tumor, releasing catecholamines. Can occur with changes in body position and exercise. Disorder can be fatal if not treated.
- Clinical features in addition to hypertension include palpitations, headache, and profuse sweating.
- Diagnosis includes biochemical testing and tumor imaging. Plasma or urine total metanephrines are good screening tools.
- Treatment: Tumor removal. Pretreatment with an α-blocker is required due to the bolus release of catecholamines during surgery.

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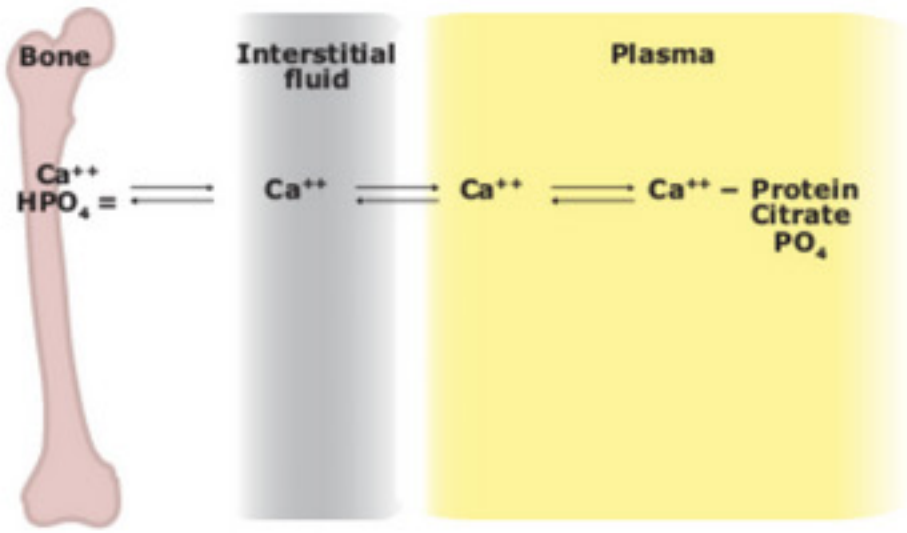
1 Introduction

- Approximately 99% of total body calcium is in bone as calcium phosphate salts, which contain hydroxide and bicarbonate ions (hydroxyapatite) in a protein matrix. Bone calcium is a reservoir that can be drawn on fairly quickly to buffer any potentially large changes in plasma calcium.



▲ **Figure 35–1.0** Compartmentalization of Calcium

- Although ECF phosphate can change twofold or threefold above or below normal without significant immediate effects, plasma-free calcium must be maintained within a very narrow range.
- Hypercalcemia causes depression of the nervous system, which includes slower reflexes. Hypocalcemia increases the excitability of the nervous system. A clinical sign is muscle tetany. This tends to occur in the hands before it develops in other parts of the body (carpopedal spasm).
- It is the free, not the bound, calcium that is the biologically active form. The interstitial fluid is almost entirely free calcium but in the plasma only about 50% is free; the remaining 50% is bound mainly to protein. Some is bound to citrate, phosphate, and other inorganic anions.
- When measuring the total calcium in plasma, plasma protein must also be measured in order to estimate the free calcium. However, a calcium electrode directly measures the free calcium.
- Plasma pH affects the bound- to free-calcium ratio. In acidemia, additional hydrogen ions are bound and buffered by the plasma proteins. The more positively charged protein drives off some calcium and raises the free fraction. More important, an alkalemia does the reverse. The increased binding of calcium to protein can induce signs of hypocalcemia.
- Phosphate circulates mainly as HPO_4^{-2} along with a small amount of $H_2PO_4^{-}$. An acidemia increases the proportion of the latter.

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2 Interrelationships of Calcium and Phosphate

- Whether calcium phosphate precipitates from solution or the precipitated salts go into solution depends on the product of their concentrations (i.e., Ca x PO_4). When this product is below some theoretical number (solubility product), calcium phosphate salts go into solution and, above this number, calcium phosphate precipitates from solution.
- Normally, plasma is close to the solubility product but inhibitors, such as pyrophosphate, prevent precipitation.
- In the fluid surrounding bone, an elevated product promotes bone deposition and a reduced product causes bone resorption.
- Soft tissues contain 10 to 12 times more phosphate than calcium. A crushing injury, such as rhabdomyolysis, can release a bolus of phosphate and raise the circulating level. A similar effect is seen in renal failure. The elevated product of their concentrations can cause precipitation of calcium phosphate, inducing a hypocalcemia.

Control: ECF free calcium is regulated by parathyroid hormone (PTH) and vitamin D. Because the body synthesizes vitamin D, it should more correctly be considered a prohormone. Three sites are involved in Ca-PO_4 homeostasis: Kidney, bone, and the GI tract. PTH acts directly on the kidney and bone, and indirectly on the GI tract through vitamin D.

3 Parathyroid Hormone

- This is the main hormone that protects against hypocalcemia. It is a peptide hormone released in response to a decrease in ECF Ca^{++}.
- The predominant cell in the parathyroids, the chief cell, monitors ECF Ca^{++} through a Ca^{++}-sensing receptor. Binding of Ca^{++} to the receptor suppresses the secretion of PTH.
- In most cells, a rise in ICF Ca^{++} initiates an exocytosis. Here, that role is played by magnesium. A hypomagnesemia can cause a temporary hypoparathyroidism.
- The relationship between the ECF Ca^{++} and PTH secretion is sigmoidal with the steep part of the curve in the physiological range for Ca^{++}. This means a small change in Ca^{++} causes a large change in PTH secretion.

Important Concept

Hyperphosphatemia often is associated with hypocalcemia; as long as the phosphate is elevated, homeostatic mechanisms have difficulty in returning the calcium toward normal. Likewise, hypophosphatemia promotes a rise in free calcium.

Because phosphate does not have to be precisely regulated, homeostatic mechanisms allow the phosphate to change as part of the precise regulation of calcium. The main determinant of plasma phosphate is its handling by the kidney.

↑ excretion of PO_4 ↓ plasma PO_4 which ↑ plasma Ca

↓ excretion of PO4 ↑ plasma PO_4 which ↓ plasma Ca

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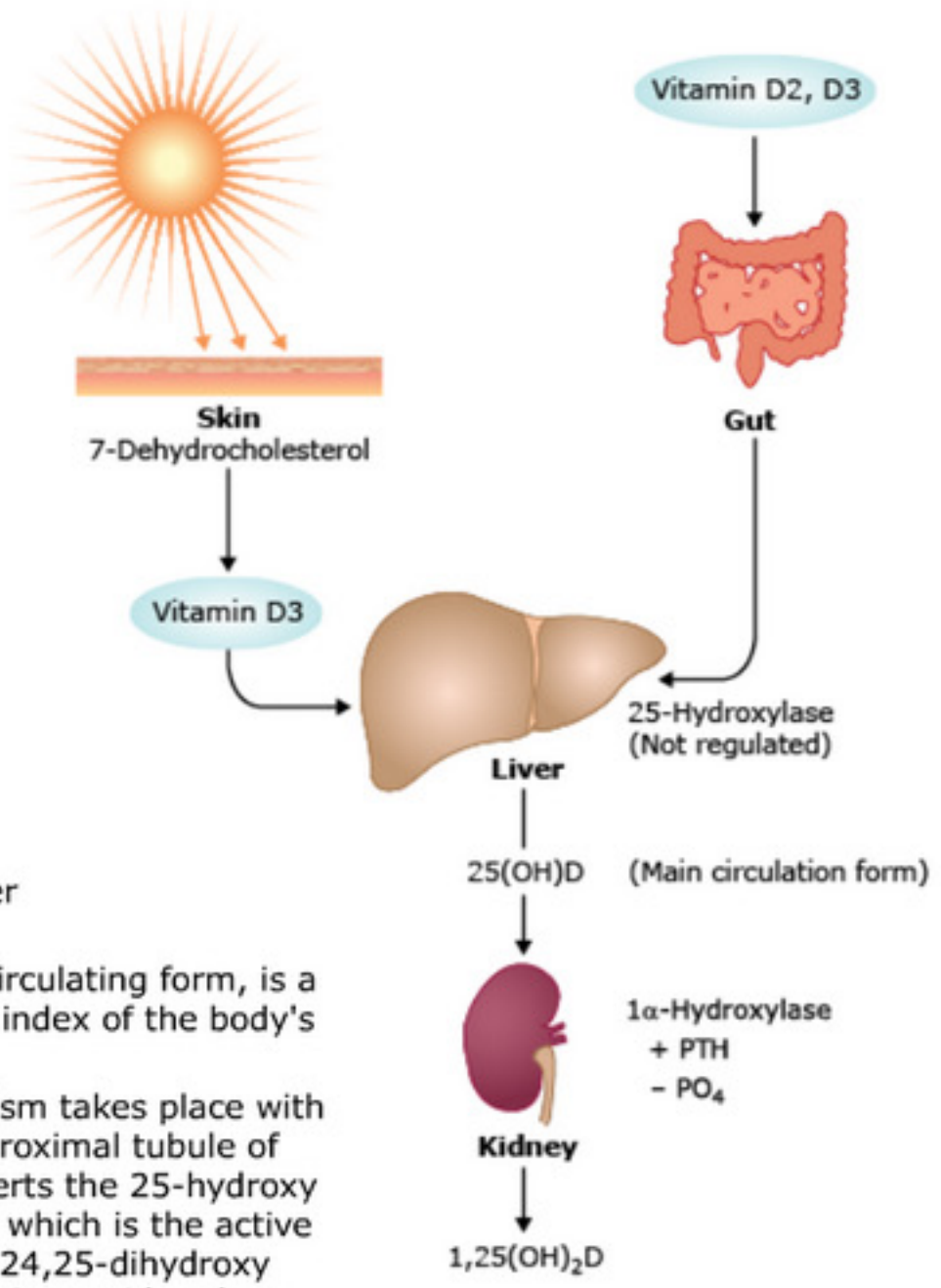
4 Vitamin D

- Plays a role in bone remodeling and renal reabsorption and GI absorption of Ca^{++} and phosphate. Vitamin D must undergo two successive hydroxylations, the first in the liver and the second in the kidney, to become the active hormonal form.
- Vitamin D3 is synthesized in the lower epidermis in response to ultraviolet light. Excessive light exposure does not produce toxic amounts of vitamin D, because long-term exposure results in the formation of inactive products. Vitamin D2 is synthesized by plants. The metabolites of both forms are equipotent.
- Vitamin D can be stored for future use mainly in adipose tissue. The lipid-soluble vitamin D is transported to the liver and converted to the 25-hydroxy form by 25-hydroxylase. It is released and circulates bound to a vitamin-D-binding protein also produced in the liver. The 25-hydroxy form has a greater affinity for the binding protein than vitamin D itself and the other vitamin D metabolites.
- 25-Hydroxyvitamin D, the main circulating form, is a good circulating reservoir and an index of the body's vitamin D reserves.
- The control of vitamin D metabolism takes place with the second hydroxylation in the proximal tubule of the kidney. 1α-Hydroxylase converts the 25-hydroxy form to the 1,25-dihydroxy form, which is the active hormonal form of vitamin D. The 24,25-dihydroxy form also produced by the kidney is considered an inactive end product.
- There is some negative feedback that affects the activity of 1α-hydroxylase (e.g., phosphate), but the activity is mainly determined by its stimulation by PTH.



▲ **Figure 35–4.0** Synthesis and Forms of Vitamin D

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5 Calcitonin

- A peptide hormone whose main known function is to inhibit osteoclast bone resorption.
- Secreted by the parafollicular C cells of the thyroid in response to elevated ECF Ca^{++}.
- It is unlikely that calcitonin plays a significant role in $Ca\text{-}PO_4$ homeostasis in humans. Loss of the thyroid (and C cells) has no effect on Ca^{++} handling or bone metabolism. The elevated secretion of calcitonin by medullary carcinoma of the thyroid C cell malignancy also has no significant effect on $Ca\text{-}PO_4$ homeostasis.
- Because calcitonin directly inhibits the activity of osteoclasts, it is useful in the treatment of Paget disease. The high bone turnover in this state is due to overactive osteoclasts.

6 PTH-Related Peptide

- A peptide paracrine hormone which is expressed in a number of tissues. It may have a role in the fetus. Adult role is unclear.
- It is structurally similar to PTH and activates the PTH receptor. It is not regulated by circulating Ca^{++} and normally has no role in $Ca\text{-}PO_4$ homeostasis.
- Secreted by some tumor cells (ectopic secretion), which causes hypercalcemia and resembles a primary hyperparathyroidism.

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7 Bone Physiology

7.1 Bone Cells

Three types of bone cells exist:

1. **Osteoblasts:** The main bone-forming cell. Expresses PTH and vitamin D receptors, and surface expression of alkaline phosphatase.
2. **Osteocytes:** Represent osteoblasts that become incorporated in the bone during remodeling. Cells contain multiple processes that connect with other osteocytes, nutrient capillaries, and bone surface osteoblasts. Their function is not fully understood. They appear to monitor regional mechanical vibration, which may affect the remodeling process. They also can absorb Ca^{++} from the fluid immediately surrounding the bone and transfer it to the bone surface and the ECF.
3. **Osteoclasts:** Multinucleated bone-resorbing cells. These arise from precursors in the monocyte lineage. Osteoblasts stimulate the formation and activation of osteoclasts via the cell surface RANKL, which stimulates the RANK receptor on the osteoclast. Other receptors also are available for osteoblast-osteoclast communication.

7.2 Bone Remodeling

- Bone remodeling is an ongoing process that peaks early in life and continuously declines thereafter. The decline accelerates in women following menopause. The weight-bearing stress experienced by bone can somewhat mitigate the decline. Training (running, not swimming) is known to have a positive effect on bone mass. Likewise, removing the gravity effect on bone (sedentary lifestyle, bed-ridden episodes, and spinal cord injury) has the opposite effect.
- Cortical bone is remodeled from within and trabecular bone from scalloped areas on the bone surface. The process is carried out by remodeling units. To resorb the bone, osteoclasts seal off an area, and secrete acids and enzymes that dissolve bone mineral and then the matrix. Following this, the osteoblasts move in. They first replace the matrix (osteoid) then mineralize (forming osteon) with Ca^{++} and PO_4 from the ECF. It should be obvious that to maintain the appropriate bone strength the overall process requires good information concerning mechanical stresses and communication between the osteoblasts and osteoclasts.
- Plasma alkaline phosphatase, an enzyme released from osteoblasts, is an index of excessive bone turnover or excessive bone loss.

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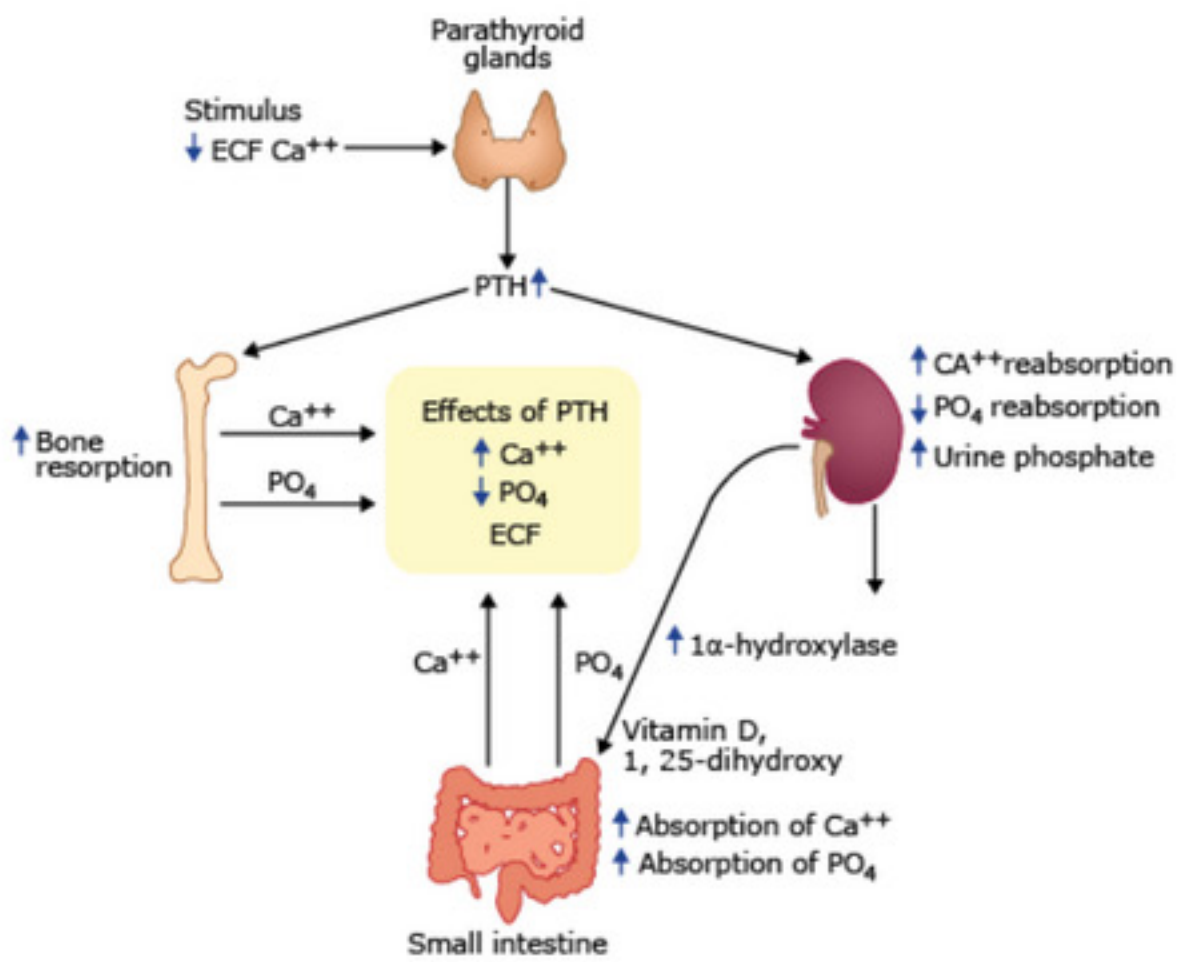
8 Regulation of ECF Calcium and Phosphate

- The PTH-vitamin D dual hormonal system is designed to defend against hypocalcemia. A decrease in ECF calcium activates the system and an elevation in calcium reduces activity.
- Targets represent three tissues: Kidney, bone, and the GI tract. They are listed in terms of how rapidly each is mobilized to defend against hypocalcemia. The overall activation is summarized in the following figure.



▲ **Figure 35–8.0** Regulation of ECF Calcium and Phosphate

Kidney: Rapid actions by PTH increase calcium reabsorption in the distal tubule and decrease phosphate reabsorption in the proximal tubule. Increasing the excretion of phosphate lowers the ECF concentration.

Bone: PTH has a rapid action followed by a slower action that mobilizes calcium from bone. A small portion of the bone contains an exchangeable fraction that is in equilibrium with the ECF on the bone surface. This is a fraction that is somewhat separated from the general ECF by bone cells. PTH acting through osteoblasts, which communicate with the trapped osteocytes, causes the calcium in the ECF in contact with the osteocytes to be pumped to the bone surface and into the general ECF. This induces some resorption to replace the lost calcium. The slower action involves the osteoblasts mobilizing and increasing the activity of osteoclasts to resorb bone. Even though phosphate is resorbed along with the calcium, the ECF concentration remains lower because of the increased excretion by the kidney.

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Note: it is the *renal* handling of phosphate that determines the ECF concentration.

GI tract: PTH acting on the proximal tubule of the kidney increases the activity of 1α-hydroxylase. This promotes the conversion of the 25-hydroxy vitamin D to the 1,25-dihydroxy vitamin D, of which the main target is the upper small intestine. Calcium is poorly absorbed by the small intestine but phosphate is readily absorbed (70%). Vitamin D increases the absorption of calcium and slightly increases the absorption of phosphate. All steps in calcium absorption are accelerated: The passive uptake across the luminal membrane, transport through the mucosal cell attached to calbindin, and the active transport at the basal membrane. Under physiological conditions, vitamin D promotes a positive calcium balance and, along with less understood actions on bone, it promotes bone deposition. Vitamin D does have an effect on the kidney to promote calcium resorption, but it is a weak effect.

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9 Pathophysiology

9.1 Primary Hyperparathyrodism

- In most cases caused by a single parathyroid adenoma (80%). The remainder generally are hyperplasia of the parathyroids. All with ↑ PTH secretion.
- Screening involves measuring plasma Ca^{++}. Overall plasma: ↑ Ca^{++}, ↓ PO_4, ↑ PTH. Also, look for both Ca^{++} and PTH in the upper normal range.
- Patients most often do not have symptoms. Determination involves an electrolyte panel with an inappropriate high Ca^{++}.
- Primary hyperparathyroidism is the main cause of hypercalcemia.
- Consequences include excessive bone turnover (↑ alkaline phosphatase). Typical consequence is osteitis fibrosa cystia. Increased scalloped areas of bone with replacement containing fibrous tissue.
- Renal function is compromised; reduced ability to concentrate the urine. Even though PTH is elevated, the filtered load of calcium is elevated and calcium appears in the urine along with diuresis, leading to dehydration. Increased cAMP in urine (second messenger of PTH).
- Symptoms of hypercalcemia, when they appear, focus on CNS depression, including: fatigue, lethargy, neuromuscular weakness, and mental depression.
- Ectopic hypersecretion is PTHrP.

9.2 Primary Hypoparathyroidism

- The problem is inadequate PTH secretion.
- The most common cause is surgery on the neck: Thyroidectomy, partial parathyroidectomy, cancer surgery.
- Plasma: ↓ PTH, ↓ Ca^{++}, ↑ PO_4. Phosphate increases because the phosphaturic effect of PTH is lost.
- Most of the symptoms occur because of hypocalcemia-induced increased neuromuscular excitability (tetany, seizures). Tetany is not unique to hypocalcemia. It also occurs with hypomagnesemia.
- Classic sign is carpopedal spasm. The muscle contractions are painful.
- Trousseau sign: Elicited from an inflated pressure cuff to 20 mmHg above systolic blood pressure. Produces carpal spasm.
- Chvostek sign: Tapping the facial nerve causes the facial muscles to contract (specificity of the test is low).

9.3 Pseudohypoparathyroidism

- Tissue resistance to PTH.
- Plasma: ↓ Ca^{++}, ↑ PO_4, ↑ PTH, Biochemical evidence similar to primary hypoparathyroidism except PTH ↑.
- Often accompanied by a somatic phenotype called Albright hereditary osteodystrophy. Features are short stature, obesity, and brachydactyly (short digits).

If a higher-than-expected Ca++ appears in the electrolyte profile, the next measurement is PTH.

Stones (kidney), bones, abdominal groans, and psychic moans.

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9.4 Secondary Hyperparathyroidism of Chronic Renal Failure

- Origin is the hyperphosphatemia of renal failure. The ↑ PO_4 induces hypocalcemia and the ↓ Ca^{++} drives a secondary hyperparathyroidism. As long as the PO_4 remains elevated, the PTH cannot elevate the plasma Ca^{++} adequately.
- Plasma: ↓ Ca^{++}, ↑ PO_4, ↑ PTH plus signs of renal failure.

9.5 Secondary Hyperparathyroidism of Vitamin D Deficiency

- Origin is a dietary deficiency in vitamin D and/or inadequate sunlight exposure, which lowers plasma calcium.
- Secondary hyperparathyroidism due to the decrease in plasma calcium.
- Plasma: ↓ Ca^{++}, ↑ PTH, ↓ PO_4. The increased excretion of PO_4 causes the ↓ plasma PO_4.
- Low plasma 25-hydroxy vitamin D diagnostic for the disorder.
- The increased PTH increases bone resorption to help maintain plasma calcium. Consequence in children is rickets, and osteomalacia in adults.
- Treatment is a vitamin D supplement to elevate circulating 25-hydroxy vitamin D.

  Note: This will not work for chronic renal failure. Because of the 1α-hydroxylase deficiency, 1,25-dihydroxy vitamin D replacement is more appropriate.

9.6 Secondary Hypoparathyroidism of Excess Vitamin D

- The excess vitamin D raises the plasma calcium, which induces the secondary hypoparathyroidism
- Plasma: ↑ Ca^{++}, ↓ PTH, ↑ PO_4. The elevated phosphate is due to the decreased phosphate excretion by the kidney.
- High plasma 25-hydroxy vitamin D is diagnostic for the disorder.
- One of the toxic effects of vitamin D is that it increases the activity of osteoclasts and increases bone resorption. As a result, there is a negative calcium balance and bone loss.

Important Concept

Under normal physiological conditions, vitamin D promotes bone deposition. However, with a deficiency in vitamin D or an excess of vitamin D there is bone loss, but for completely different reasons.

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9.7 Hypercalcemia vs. Hypocalcemia

9.7.1 Hypercalcemic States

- The symptoms of hypercalcemia as presented for primary hyperparathyroidism.
- The physiological defense for hypercalcemia is suppression of PTH.
- The kidney plays an adaptive role. The filtered load of calcium increases and combined with a decrease in PTH results in a calciuria and a washout of calcium. May be accompanied by a polyuria and some dehydration. The kidney is the only route for the elimination of the ECF calcium other than deposits of calcium phosphate in bone and soft tissues.
- Disorders
  1. Primary hyperparathyroidism:* ↑ Ca^{++}, ↓ PO_4, ↑ PTH
  2. Vitamin D intoxication: ↑ Ca^{++}, ↑ PO_4, ↓ PTH
  3. Thyrotoxicosis: Mild ↑ Ca^{++}, ↓ PTH
  4. Immobilization: Mild ↑ Ca^{++}, ↓ PTH

  *One of the key disorders for the exam.

  Note: One common, long-term feature of hypercalcemic disorders is bone loss. The only exception is milk-alkali syndrome.

9.7.2 Hypocalcemic States

- The classic symptom, as mentioned with primary hypoparathyroidism, is muscular tetany.
- The physiological defense is increased secretion of PTH. Hypocalcemic disorders are best understood as intrinsic failures within the PTH-vitamin D system.
- Disorders
  1. Vitamin D deficiency:* ↓ Ca^{++}, ↓ PO_4, ↑ PTH
  2. Primary hypoparathyroidism:* ↓ Ca^{++}, ↑ PO_4, ↓ PTH
  3. Chronic renal failure: ↓ Ca^{++}, ↑ PO_4, ↑ PTH + other signs of renal failure
  4. Pseudohypoparathyroidism: ↓ Ca^{++}, ↑ PO_4, ↑ PTH

  *One of the key disorders for the exam.

9.8 Osteomalacia vs. Osteoporosis

- Osteomalacia and rickets represent disorders in which there is inadequate mineralization of bone matrix. Rickets occurs before plate closure; osteomalacia occurs after plate closure. Rickets often develops into a bowing of the legs.
- Osteoporosis is a chronic loss of bone mass, which includes a demineralization and loss of bone matrix. Initial loss of bone mass osteopenia. Associated with age-related changes in bone structure. Plasma: Ca^{++}, PO_4, PTH all in the normal range.

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1 Introduction

- Thyroid hormones, under normal conditions, are considered anabolic (promote protein synthesis). They act on all cells and tissues with many direct actions and in other subtle ways to facilitate the actions of other hormones and neurotransmitters. They are required for the synthesis and secretion of growth hormone, and there is a synergy between catecholamines and thyroid hormones.
- Synthesis of thyroid hormones requires iodide (I^-) or iodate, which is converted to iodide in the stomach. Iodine (I^0) in the diet is not a substitute.
- A dietary deficiency in iodide is a daily intake of less than 100 µg/day. A goiter develops when intake decreases to less than 50 µg/day; however, the individual remains euthyroid. An extreme deficiency leads to hypothyroidism.
- Almost all the loss of body iodide is in the urine. In a steady state, the daily intake equals the loss of iodide in the urine. Urinary iodide is a good index of dietary intake.

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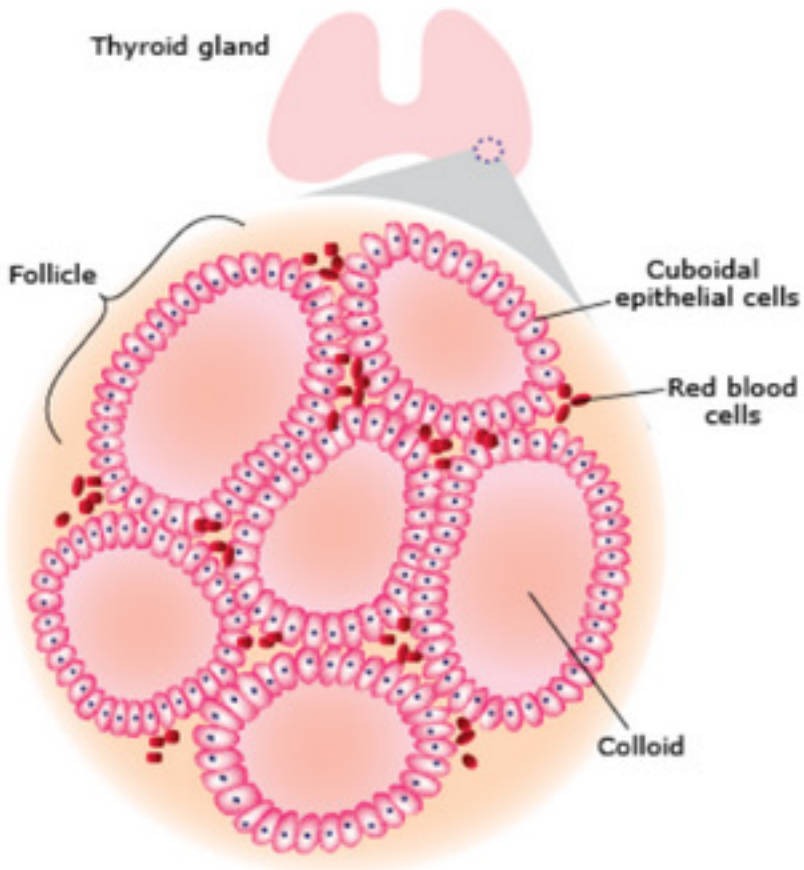
2 The Thyroid Follicle

The thyroid follicle is the functional unit of the thyroid. It is a spherical structure about 250 μm in diameter. The lumen is filled with colloid (i.e., thyroglobulin) with several months' supply of thyroid hormones covalently bound. In addition, a large reservoir of iodine is bound to tyrosine residues, which are available for future thyroid hormone synthesis.

Surrounding the follicle lumen is a single layer of epithelial cells that function in both the synthesis and the secretion of thyroid hormones.



▲ **Figure 36–2.0** The Thyroid Follicle

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3 Synthesis and Secretion of Thyroid Hormones

Two substrates are required for synthesis: Iodide and thyroglobulin.

3.1 Iodide

- Average daily intake is about 400 µg. The iodide is actively taken up by the follicle cells by secondary active transport ($2Na^+$-$1I^-$—sodium iodide symporter, NIS).
- NIS also is expressed in the placenta, salivary glands, and actively lactating breast but there is no organification.
- Low iodide intake increases the uptake of I^- and high iodide intake suppresses the I^- uptake by the follicle cells and the enzymatic synthesis of thyroid hormone. This autoregulatory control is known as the Wolff-Chaikoff effect. The suppressive effect of a high intake of I^- is transient and the normal thyroid escapes after 10 to 14 days. In autoimmune thyroiditis and certain other disorders leading to hypothyroidism, the thyroid may be incapable of the escape phenomenon.
- The rate of I^- uptake by the thyroid is an index of thyroid function. A decreased rate of uptake occurs in hypothyroidism and an accelerated rate in hyperthyroidism. A gamma detector placed over the thyroid asseses the rate of uptake of I^{123} or I^{131}. Twenty-four hours later, the distribution of the iodide can be imaged for uniformity, cold spots, and hot spots.
- Iodide taken up by the follicle cells is passively transported by a protein carrier called pendrin across the apical membrane into the follicle lumen. All steps in the synthesis of thyroid hormone take place in the follicle lumen adjacent to the inner apical membrane.

3.2 Thyroglobulin

- A glycoprotein synthesized by the follicle cells.
- Thyroid hormone synthesis involves iodination and coupling of the amino acid tyrosine ring structures called *residues*.
- A thyroglobulin molecule has about 140 tyrosine residues, but only a few are oriented for effective coupling to form T_3 and T_4. The remaining residues attach iodine-forming mainly diiodotyrosine and some monoiodotyrosine, and the iodine as such represents a large reservoir which defends against a dietary deficiency.
- Thyroglobulin is extruded into the follicle lumen by an exocytosis.

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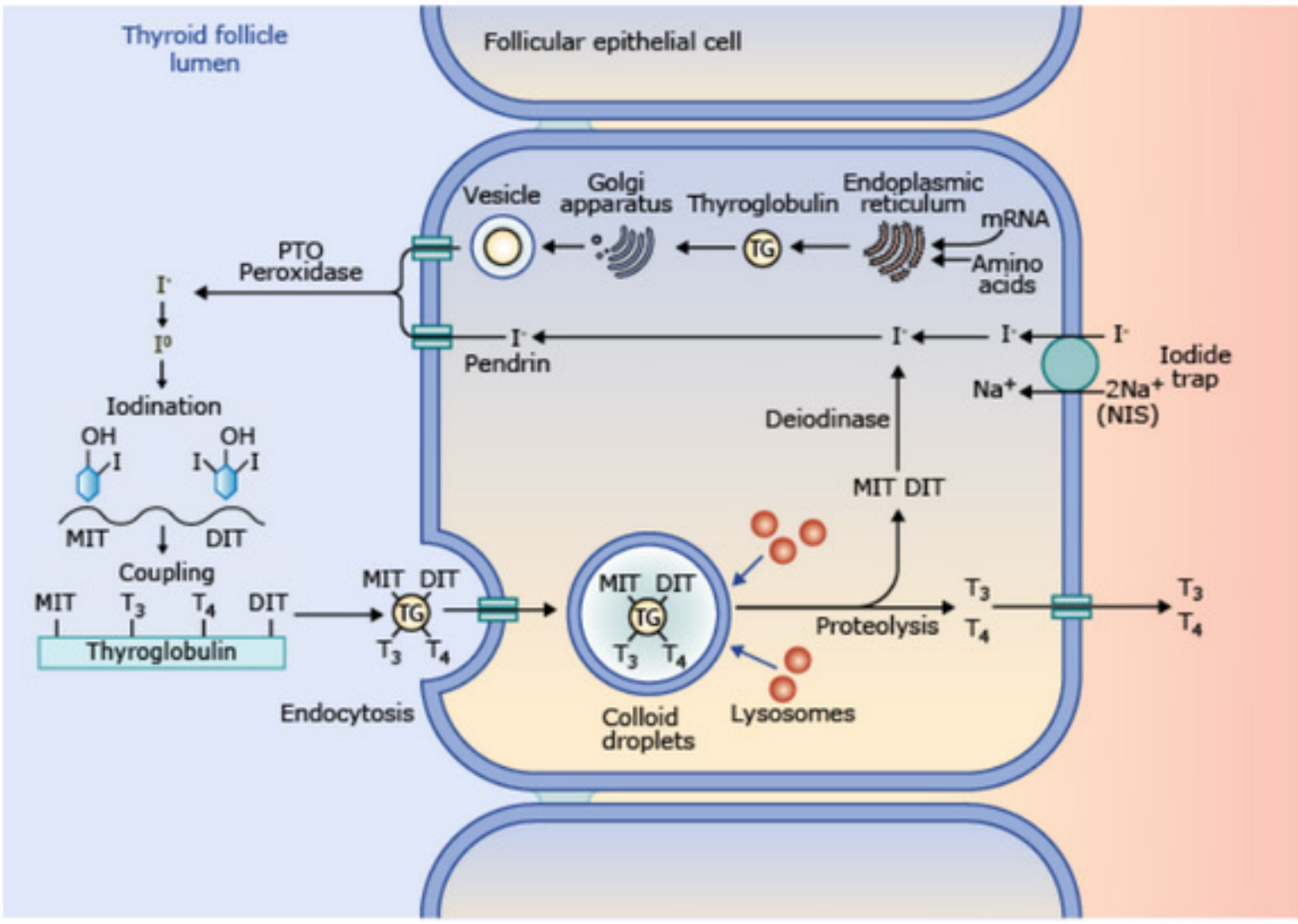
3.3 Steps in the Synthesis



▲ **Figure 36–3.3** The Synthesis, Storage, and Secretion of Thyroid Hormones

There are three steps in the synthesis of thyroid hormones: Oxidation of I^- to I^0, organification-iodination of tyrosine residues, and coupling of two residues to form T_4 and T_3. All steps in the synthesis are catalyzed by thyroid peroxidase (TPO).

- **Step 1:** The I^- is oxidized to I^0 with locally produced hydrogen peroxide.
- **Step 2:** Organification. Each tyrosine residue can take up a maximum of two iodines. Without an iodine deficiency, most residues attach two iodines (diiodotyrosine, DIT). Only a few attach one iodine (monoiodotyrosine, MIT). With an iodine-deficient diet, the production of monoiodotyrosine probably increases.
- **Step 3:** Tyrosine residue coupling. The final step only involves a few of the iodinated tyrosine residues. If two DITs couple, the end product is T_4. If a DIT couples with an MIT, the end product is usually T_3. In a very small percentage of the cases, the end product would be rT_3. In an iodine deficiency, a greater synthesis of MIT also would mean a greater synthesis of T_3. However, the main end product would remain T_4.
- The thyroglobulin with attached T_4, T_3, rT_3, DIT, and MIT is stored within the follicle lumen.

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3.4 Secretion of Thyroid Hormone

- Thyroglobulin reenters the follicle cell by the process of endocytosis.
- The membrane-bound thyroglobulin then fuses with lysosomes. The lysosomal enzymes digest the thyroglobulin and release T_4, T_3, DIT, MIT, peptides, and individual amino acids.
- DIT and MIT are deiodinated by a deiodinase that does not act on T_4 or T_3. The iodine is then recycled. Very little is lost to the circulation. Loss of significant DIT and MIT iodine promotes an iodine deficiency.
- T_4 and T_3 are released to the circulation. A few other end products and a small amount of thyroglobulin also are released. Circulating thyroglobulin increases in thyroiditis, nodular goiter, and Graves disease.

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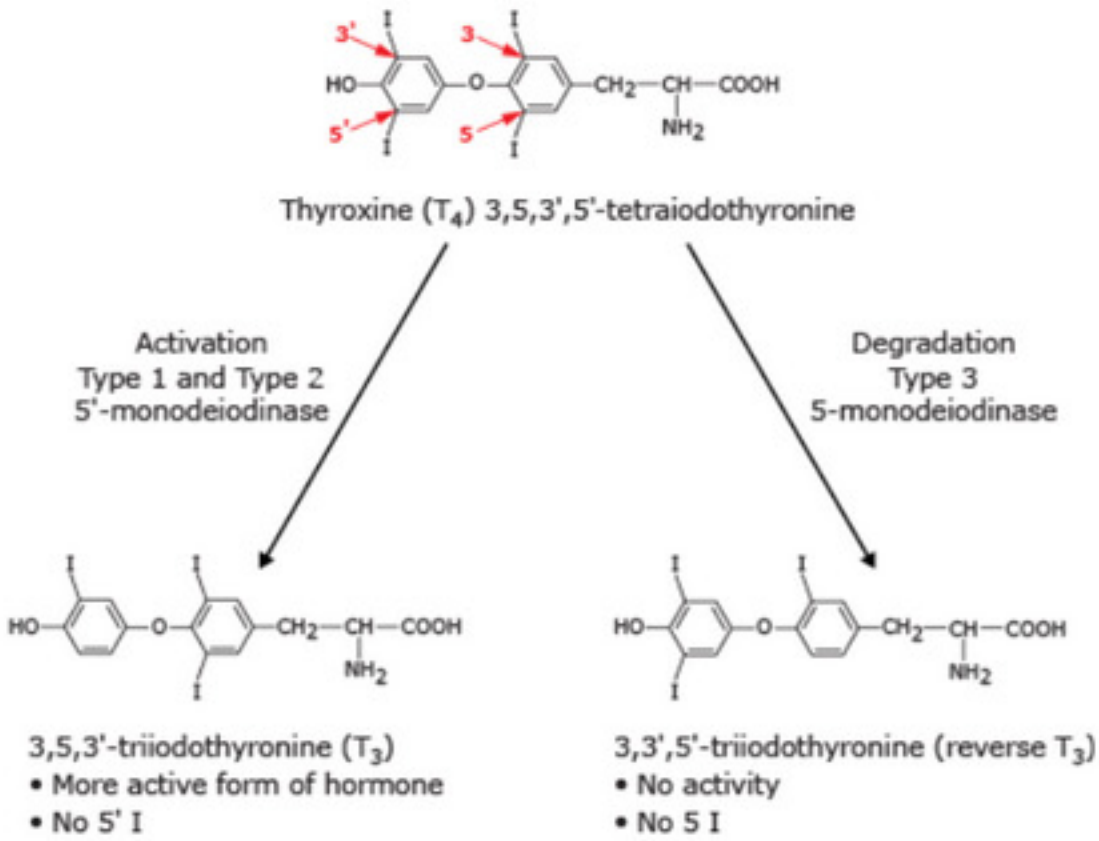
4 Iodothyronine Structure and Activity

- Thyroid hormones are secreted in the same proportion as they are synthesized and stored. The main end product and secretion of the thyroid is T_4. About 20 T_4 are released for every T_3. The release of rT_3 is insignificant.
- T_4 and T_3 attach to the same nuclear receptor. T_3 has the higher affinity for the receptor and thus is the more active form of the hormone. In fact, many now consider T_4 to be a circulating prohormone with its conversion to T_3 or rT_3 determining the circulating and peripheral tissue activity.
- Three separate deiodinases act on T4:

Type 1 5′-monodeiodinase: Found mainly in the liver, kidney, and skeletal muscle. This enzyme has a low affinity for T_4. It removes an iodine from the outer ring of T_4 and its major function is to provide T_3 to the circulation. Most of the circulating T_3 is derived from the peripheral conversion of T_4.

Type 2 5′-monodeiodinase: Found mainly in the brain and in the thyrotropes of the anterior pituitary. High affinity for T_4 and it maintains a constant T_3 for the central nervous system. Within the thyrotropes, T_4 must be converted to T_3 before it exerts any negative feedback effect.



▲ **Figure 36–4.0** Conversion to T_4 to T_3 and Reverse T_3

Type 3 5-monodeiodinase: Acts on the inner ring of T_4 to remove an iodine. Converts the T_4 into rT_3 or T_3 into T_2. These end products have no known biological function.

The activity of the deiodinases have important physiological actions:

1. Permit peripheral modulation of thyroid hormone action.
2. Helps the individual adapt to changing states, such as an iodine deficiency, by increasing the conversion to T_3 to maintain the euthyroid state. The opposite occurs in stresses, such as starvation and illnesses, to reduce the metabolic rate and conserve energy (low T_3 syndrome).

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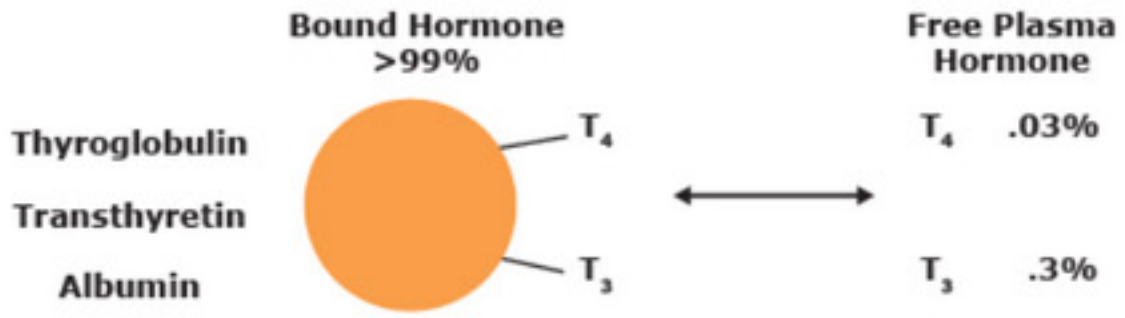
5 Thyroid Hormone Transport



▲ **Figure 36–5.0** Transport of Thyroid Hormones

- T_4 and T_3 circulate tightly bound to protein. Only about 0.03% of the T_4 and 0.3% of the T_3 is free in the circulation. Bound T_4 constitutes a significant reservoir and buffers any transient changes in T_4 secretion.
- Three proteins bind and transport thyroid hormones: Thyroid-binding globulin (TBG); thyroid-binding prealbumin, called transthyretin; and albumin.
- TBG has a single site to bind T_4 or T_3. Because T_4 is bound more strongly, it has the longer half-life, seven days as opposed to one day for T_3. A congenital deficiency in TBG decreases the total T_4 in the circulation, but the free T_4 is normal and the individual is euthyroid.
- TBG increases in pregnancy, estrogen secreting tumors, and estrogen therapy.
- TBG is decreased by androgens, nephrotic syndrome, and liver disease.

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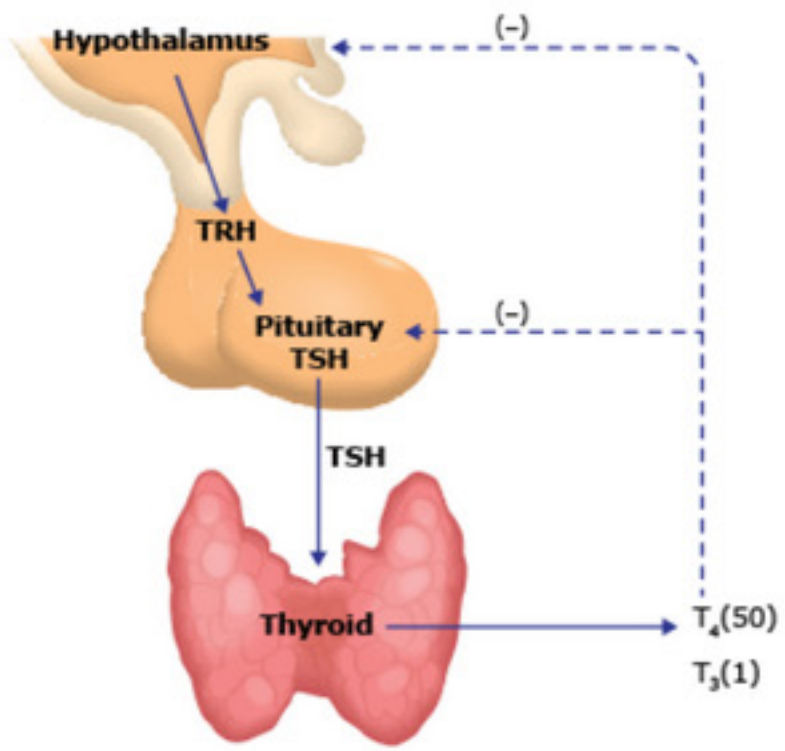
6 Regulation of Thyroid Hormone Secretion

- TSH stimulates every aspect of thyroid function. It accelerates all steps in hormone synthesis and degradation of thyroglobulin leading to the release of hormone to the circulation.
- Increased TSH causes capillary proliferation and long-term hyperplasia or hypertrophy of the thyroid, leading to a goiter. A goiter is, by definition, an enlarged thyroid. It does not designate function status. A goiter can develop in hyper- and hypothyroidism, and in the euthyroid state with an iodinedeficient diet.
- Like all the hypothalamic-anterior pituitary systems, TRH and TSH secretion is pulsatile, but because of the long half-life of TSH, plasma levels are stable. A single plasma sample is a good index of overall TSH secretion.



▲ **Figure 36–6.0** Regulation of the Thyroid System

- TRH provides the stimulus to secrete TSH from the anterior pituitary thyrotropes. The TSH target is the thyroid, where it stimulates the secretion of T_4 and T_3.
- Both the circulating free T_4 and T_3 create a negative feedback loop. They act at the level of the hypothalamus but mainly at the level of the anterior pituitary.
- Because the main circulating form is T_4 (50 T_4 to 1 T_3), most of the negative feedback is due to circulating T_4. T_4 within the thyrotropes is rapidly converted into T_3 by type 2 5′-monodeiodinase. It is the T_3 that acts to reduce the sensitivity of the thyrotropes to TRH.

Generalization: As long as the circulating free T_4 is constant, there is a constant negative feedback and a constant secretion and circulating level of TSH. However, most of the circulating activity is due to T_3. In low T_3 syndrome, metabolic rate is reduced, but because T_4 is unchanged, TSH remains in the normal range.

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7 Physiological Actions of Thyroid Hormones

- Thyroid hormones increase the basal metabolic rate and, thus, oxygen consumption and heat production. Hyperthyroidism is associated with heat intolerance and hypothyroidism with cold intolerance. The increased metabolic action of thyroid hormones is in part due to the increase in the activity of membrane-bound Na^+/K^+-ATPase. There is also an increased protein turnover (increased amino acids released from skeletal muscle). The transcriptional effect of T_3 demonstrates a lag of hours or days to achieve a full effect. Thyroid hormones do not affect the metabolic rate of the testes, uterus, or nervous tissue.
- There is a synergism between catecholamines and thyroid hormones. In the heart, there is both an inotropic and chronotropic effect. Thyroid hormone increases β receptors in the heart, skeletal muscle, and adipose tissue. Many of the clinical consequences of thyrotoxicosis appear to reflect an increased sensitivity to catecholamines. Thyroid storm is an accentuation of the symptoms of thyrotoxicosis without, in many cases, a demonstrable increase in circulating T_3 or T_4. Symptoms are relieved by propranolol, which blocks β receptors as well as inhibiting the conversion of T_4 to T_3.
- Thyroid hormones play a permissive role in the normal ovarian cycle and spermatogenesis. Hypothyroidism leads to menstrual irregularities (menorrhagia) and promotes infertility (anovulatory cycles).
- Thyroid hormones increase the absorption of glucose from the small intestine and increase gut motility. There is an increase in bowel movements in hyperthyroidism and a decrease in hypothyroidism (constipation).
- Thyroid hormones are necessary to convert carotene to vitamin A. As such, hypothyroidism is associated with yellowing of the skin and night blindness.

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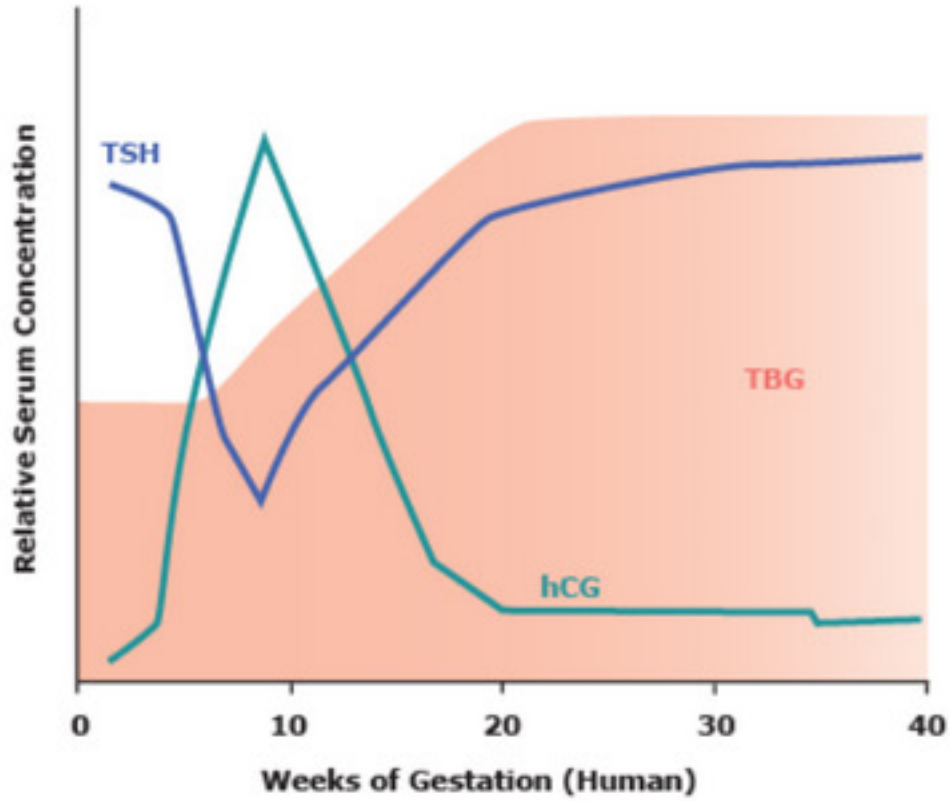
8 Thyroid Hormone in Pregnancy

- There are a number of changes in the thyroid axis during pregnancy. There is a greater urine iodide clearance. A low iodide intake can cause a maternal goiter. This occurs in part as a result of placental type 3 5-monodeiodinase increasing the turnover of T_4. Hypothyroid women require a higher dose of replacement hormone during pregnancy. Due to estrogen stimulation of TBG production, total T_4 increases. Maternal hCG, which is a weak TSH receptor agonist, peaks in the first two months of pregnancy, causing a slightly elevated free T_4 and a modest suppression of TSH. This increase in free T_4 is not consistently presented in the literature. Pathological increases in hCG can cause hyperthyroidism.
- In the fetus, thyroid hormone secretion begins about midgestation. TSH then increases rapidly and T_4 peaks near the end of gestation. Following delivery, there is a further rise in T_4 and T_3.
- Placental type 3 5-monodeiodinase prevents much of the maternal thyroid hormones from crossing the placental barrier. However, what is delivered can be important in fetal brain development. Euthyroid infants who are delivered by hypothyroid mothers or those who have been inadequately treated for hypothyroidism during pregnancy may have a diminished intellectual potential later in childhood. This strongly emphasizes the importance of maintaining the mother in a euthyroid state during pregnancy.



▲ **Figure 36–8.0** The Thyroid System During Pregnancy

- A hypothyroid fetus appears to develop normally and has a normal birth weight, and few newborns are diagnosed as hypothyroid based on clinical features. Features that may be present, however, include prolonged jaundice, hoarse cry, marked retardation of bone maturation, and feeding problems.
- Without the presence of thyroid hormone soon after delivery, irreversible abnormalities develop in brain maturation. These changes lead to mental retardation. Consequently, neonatal screening is required following delivery for either TSH or T_4 in heel-prick blood specimens taken 24 to 48 hours following delivery. When a diagnosis is confirmed, treatment is immediately instituted. T_4 requirements are relatively great during the first year of life.

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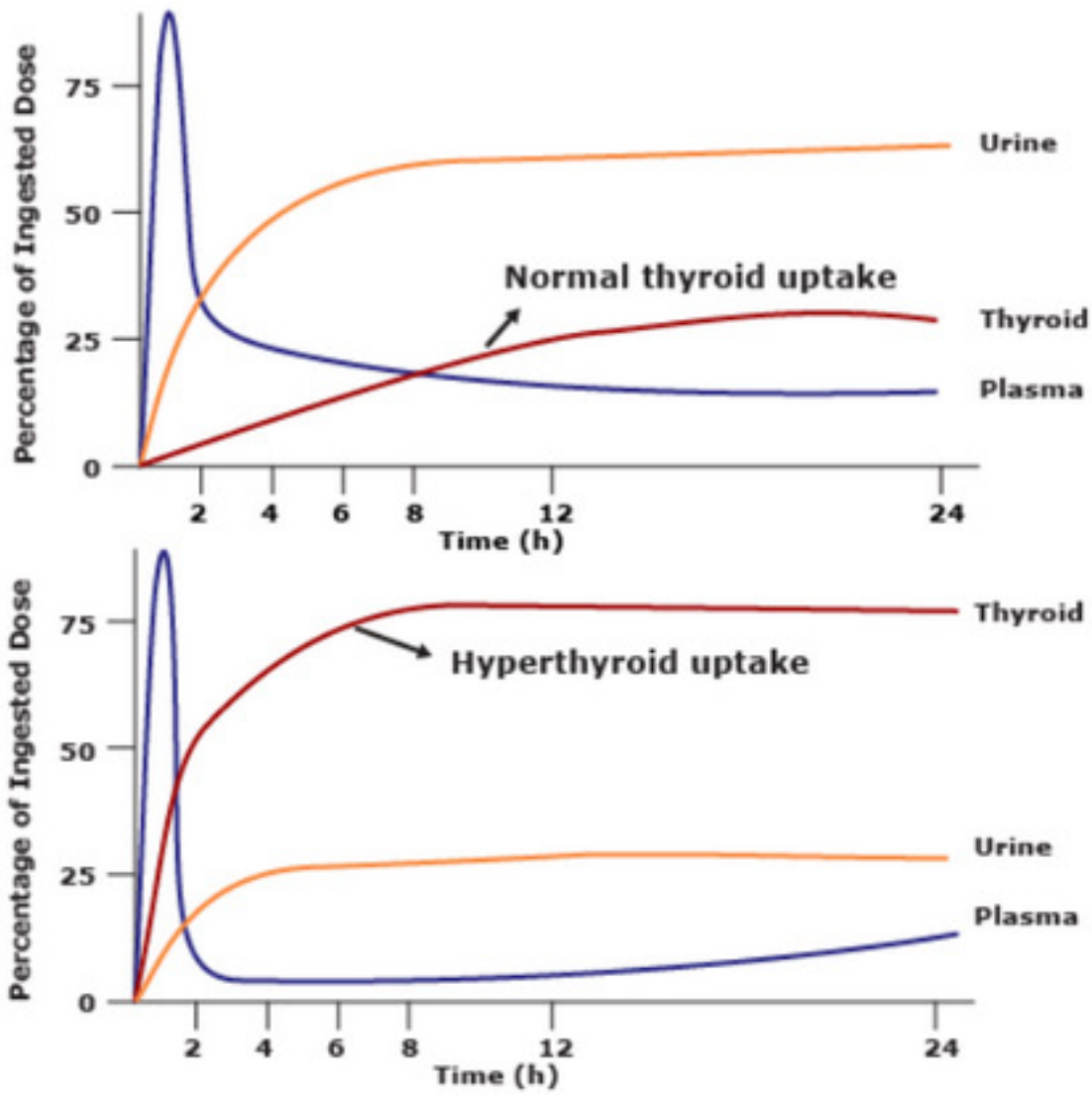
9 Tests of Thyroid Function

- Thyroid dysfunction generally arises from primary disorders of the gland. If there is no suspicion of dysfunction, measurement of TSH alone is adequate. It is a low-cost, but highly sensitive, test.
- When suspicions of a thyroid problem exist, free T_4 should be measured along with TSH. Total T_4 is not an adequate index of free T_4. Measurement of TSH with free T_4 may reveal even mild forms of dysfunction when the TSH and T_4 are still in the normal range (subclinical hypothyroidism, TSH upper range of normal, and free T_4 lower range of normal).
- Autoimmune thyroid disease can be detected by measuring circulating antibodies. A small percentage of euthyroid individuals have these antibodies and they should be considered at increased risk for thyroid disease. Most patients with autoimmune hypo- and hyperthyroid disease have TPO antibodies. Graves disease, in addition, has TSI antibodies that stimulate the TSH receptor.
- Subclinical hypothyroidism is usually the early stage of Hashimoto thyroiditis. It is confirmed by measuring TPO antibodies.



▲ **Figure 36–9.1A** Iodide Dynamics in the Euthyroid and Hyperthyroid States

- Because the signs of mild or subclinical hypothyroidism go undetected or are absent, it is recommended that screening for hypothyroidism be undertaken in high-risk groups, such as elderly women.

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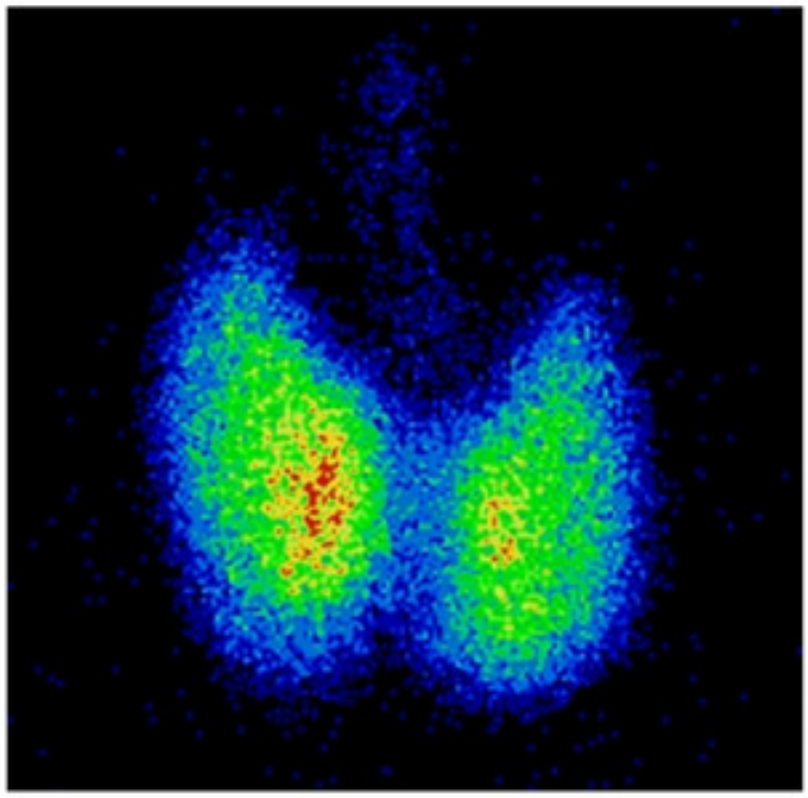
- Serum thyroglobulin (TG) is elevated in almost all types of thyrotoxicosis. It is more highly elevated in all types of thyroiditis, indicating damage and destruction of the thyroid tissue. The normal thyroid releases small amounts of detectable TG. However, following complete ablation, TG should fall to below detectable levels.
- Radioiodide uptake can separate the various causes of thyrotoxicosis. Iodine-123, with only a half-life of 13 hours, is ideal for this purpose.



▲ **Figure 36–9.1B** Scan of Radioactive Iodide Uptake by the Thyroid—Graves Disease

- Graves disease is associated with an accelerated uptake of iodide, which is uniformly distributed throughout the thyroid.
- Toxic multinodular goiter has areas of high uptake and areas of low uptake along with an abnormal architecture of the thyroid.
- Toxic adenomas create local areas of high uptake but the remainder of the gland is associated with low uptake.

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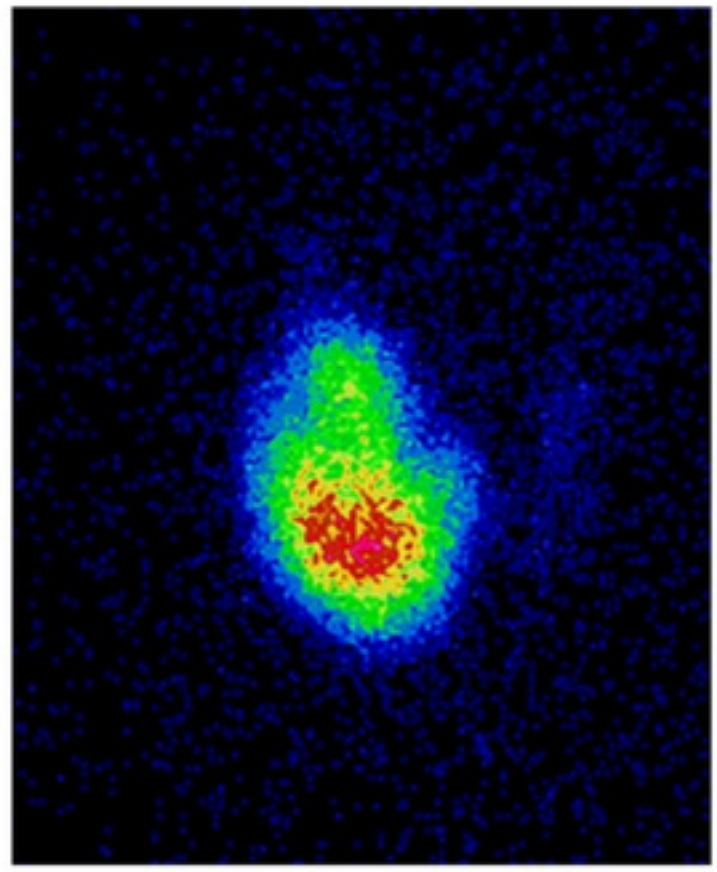
10 Hypothyroidism

- Almost always a primary disorder of the thyroid gland. Hashimoto thyroiditis is the most common cause.
- Characterized by an ↑ TSH and ↓ free T4. Secondary or tertiary hypothyroidism rarely is an isolated disorder. If present, they usually are associated with pituitary or hypothalamic disease (↓ TSH, ↓ free T4).

  Note: Measurement of TSH is not reflective of thyroid function in patients with pituitary disease.
- Reduced feedback of T4 to the hypothalamus increases TRH, which drives a hyperprolactinemia. The elevated prolactin may contribute to decreased fertility and reduced libido in men and women.
- Hashimoto thyroiditis may be associated with or without a goiter. Younger patients are more likely to present with goiter. In older patients, the thyroid may have undergone complete destruction but with retention of a positive test for TPO antibodies.
- Early-stage autoimmune disease is particularly susceptible to excessive iodide intake (no escape from Wolff-Chaikoff effect). Lithium and amiodarone also can block hormone synthesis. In cases of reduced hormone synthesis, a goiter is common.
- Decreased metabolic rate, decreased body temperature, cold intolerance, and increased weight gain without increased food intake.
- Slowed speech and thought processes. Extreme cases have severe mental symptoms (myxedema madness).
- Decreased sweating, dry skin, puffy features, loss of hair, lowering of upper eyelids, hoarse voice, enlarged tongue.
- Inability to convert carotene to vitamin A causes yellowing of the skin and night blindness.
- Shallow, low respiratory rate; muscle cramps; slowed reflexes, particularly deep tendon reflexes with slow relaxation phase.
- Interstitial accumulation of mucopolysaccharides with a non-pitting edema (myxedema).
- Anemia, constipation, ↓ adrenergic activity with ↓ chronotropic and inotropic effects.
- Myxedema coma is the end result of untreated hypothyroidism. There is a progressive weakness, stupor, hyponatremia, hypoglycemia, and hypoventilation. Hypothermia may be severe. Most often develops in obese, elderly women in the winter. Fatal if not successfully treated.



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▲ **Figure 36–11.0** Scan of Radioactive Iodide Uptake by the Thyroid—Toxic Adenoma

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- Iodide deficiency if not severe; patient is euthyroid. Increased conversion of T_4 to T_3 maintains the euthyroid state. Because of a reduced circulating T_4, TSH increases, in some cases driving an extremely large goiter.
- Replacement therapy with T_4 is curative. Replacement with T_3 generally is inappropriate. There is adequate peripheral conversion of T_4 to T_3. Giving T_3 would, in many cases, elevate the circulating T_3 above physiological levels.
- Cretinism is untreated congenital hypothyroidism. It is characterized by slowed growth and short stature, which is a form of dwarfism and mental retardation. The main cause worldwide is severe iodide deficiency. Typically, the thyroid fails to descend during embryonic development from its origin at the base of the tongue to the appropriate neck region (ectopic thyroid).

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11 Thyrotoxicosis and Hyperthyroidism

- Thyrotoxicosis is the clinical state whereby tissues are exposed to excessively high circulating thyroid hormones. Generally, it is caused by a primary hyperthyroidism and the most common is Graves disease.
- Graves disease is associated with the production of autoantibodies (TSI: thyroid-stimulating immunoglobulins) that stimulate the TSH receptor. Laboratory findings would include ↑ T_4, but ↓ TSH.
- TSI stimulation often produces a diffuse, firm goiter as a result of hyperplasia and hypertrophy. A radionuclide scan shows a uniform iodide uptake. This would separate Graves from a nodular thyroid disease.
- There is an underlying genetic predisposition, but it is not evident what initiates Graves disease. Some possibilities include excess iodide, viral or bacterial infections, and psychological stress.
- The symptoms of Graves disease are basically the opposite of those found in hypothyroidism and are as follows:
  - Increased metabolic processes, ↑ oxygen consumption, ↑ heat production, heat intolerance, ↓ body weight despite increased food intake. Increased amino acid release from skeletal muscle creates a negative nitrogen balance and muscle weakness, which can be severe.
  - Increased adrenergic activity causing ↑ chronotropic (sinus tachycardia) and ↑ inotropic effects. However, the circulating levels of epinephrine and norepinephrine are not elevated. Thus, there appears to be an increased sensitivity to catecholamines. There is a thyroid hormone-mediated increase in membrane-bound, β-adrenergic receptors.
  - Tremor, nervousness, excessive sweating, palpitations, and dyspnea on exertion. In children, rapid growth with accelerated bone maturation.
  - Exopthalmos (abnormal protrusion of the eyeballs) and periorbital edema.
  - Thyrotoxic crisis (thyroid storm) is the acute exacerbation of the symptoms of thyrotoxicosis, which can be life threatening. Manifestations include a hypermetabolism with fever, flushing, and excessive sweating. Elevated adrenergic effects such as tachycardia and, in some cases, atrial fibrillation, elevated contractility, and a widened pulse pressure. It once was believed that thyroid storm was an excessive dumping of thyroid hormone or sudden elevation of T_3 in the circulation. Currently, there is no clear evidence of such a mechanism. Instead, it may be a stress-induced, elevated adrenergic response. Propranolol is a standard treatment. It not only blocks the β receptors but it reduces the conversion of T_4 to T_3.
- Treatment of Graves disease involves ablation of the thyroid either by the radiation effects of iodine-131 or by surgery. Surgical removal often causes a massive release of hormone and is not the preferred treatment. Outside the United States, primary antithyroid drug treatment is preferred.

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12 Other Causes of Thyrotoxicosis

- TSH-secreting adenoma of the anterior pituitary causing a secondary hyperthyroidism is rare (↑ TSH, ↑ T_4).
- Ectopic thyroid-hormone-secreting tissue, teratomas of the ovary (struma ovarii) also rare (↓ TSH, ↑ T_4).
- Toxic adenomas autonomously secreting T_4 and T_3. Suppresses TSH and there is reduced function and iodide uptake of the normal glandular regions.
- Toxic multinodular goiter usually develops in older patients with long-standing euthyroid multinodular goiter (↓ TSH, ↑ T_4, and T_3). Scan reveals patchy, irregular distribution of radioactive iodide.
- Amiodarone induced thyrotoxicosis. A class III antiarrhythmic that contains 37% iodide. Thyroidtoxicosis can be due to excessive iodide or an amiodarone thyroiditis with inflammation and release of T_4 and T_3.
- Subacute thyroiditis: Can cause the release of thyroid hormone. In this case it is an acute inflammation disorder, probably due to a viral infection (↓ TSH, ↑ T_4).

13 Goiter

- A goiter by definition is an enlarged thyroid. It does not designate functional status. Goiters exist in hypo-, hyper-, and in euthryoid states.

  Note: There is no correlation between thyroid size and function.
- Goiters often are classified as diffuse (general enlargement) or nodular. Nodular disease is associated with a disordered growth of thyroid tissues often combined with a slow fibrosis.
- A diffuse goiter develops in Hashimoto thyroiditis, Graves disease, and with an iodide deficiency. A diffuse goiter often results from a chronic overstimulation of the thyroid by TSH or, in the case of Graves disease, TSI. A diffuse goiter eventually can develop into a nodular goiter.
- Nodular disease is common. Thyroid nodules may be solitary or multiple. They may be functional (toxic) or nonfunctional.

▼Table 36–13.0 Summary of Basic Thyroid Disorders

	FT4	TSH
1° Hyperthyroidism	↑	↓
2° Hyperthyroidism	↑	↑
1° Hypothyroidism (Hashimoto)	↓	↑
2° Hypothyroidism	↓	↓

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1 Testicular Function

1.1 Organization of the Testes

- The testes reside in the scrotum outside the abdominal cavity where the temperature is about 2°C lower, a requirement for normal spermatogenesis.
- Spermatogenesis takes place within the epithelial cells (Sertoli cells) lining the seminiferous tubules. These structures account for about half of the testicular mass. The Sertoli cells form tight junctions with other Sertoli cells. Tight junctions prevent the passage of proteins from the interstitial spaces into the lumen of the seminiferous tubules (blood-testes barrier). This creates an immunologically safe environment for the developing sperm.
- The seminiferous tubules empty into a network of ducts called the rete testis and then to the single-duct epididymis, which serves as a reservoir for the sperm.
- Spermatogenesis requires normally functioning Sertoli cells and the interstitial cells of Leydig.

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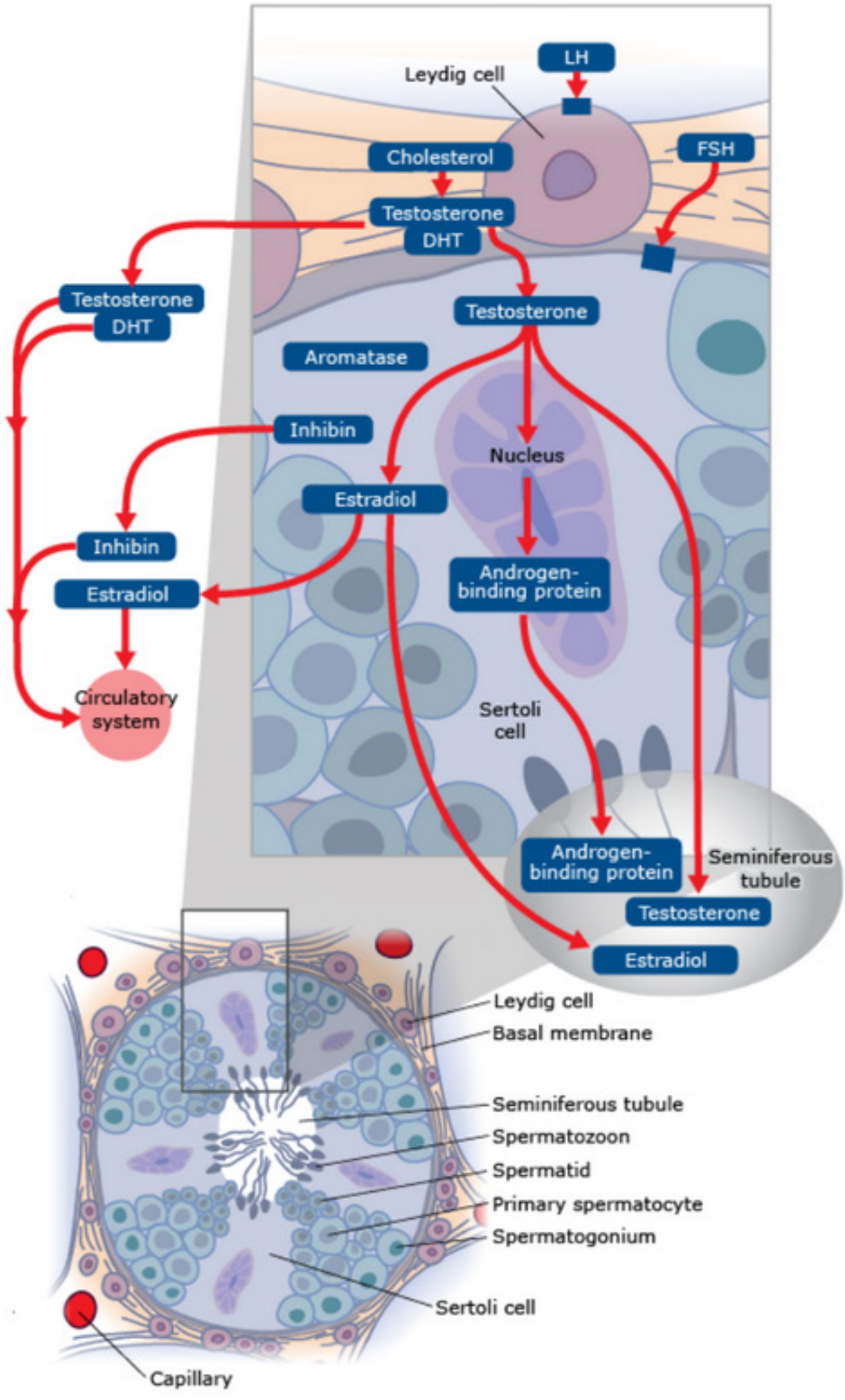

▲ **Figure 37–1.1** The Male Reproductive Hormone System

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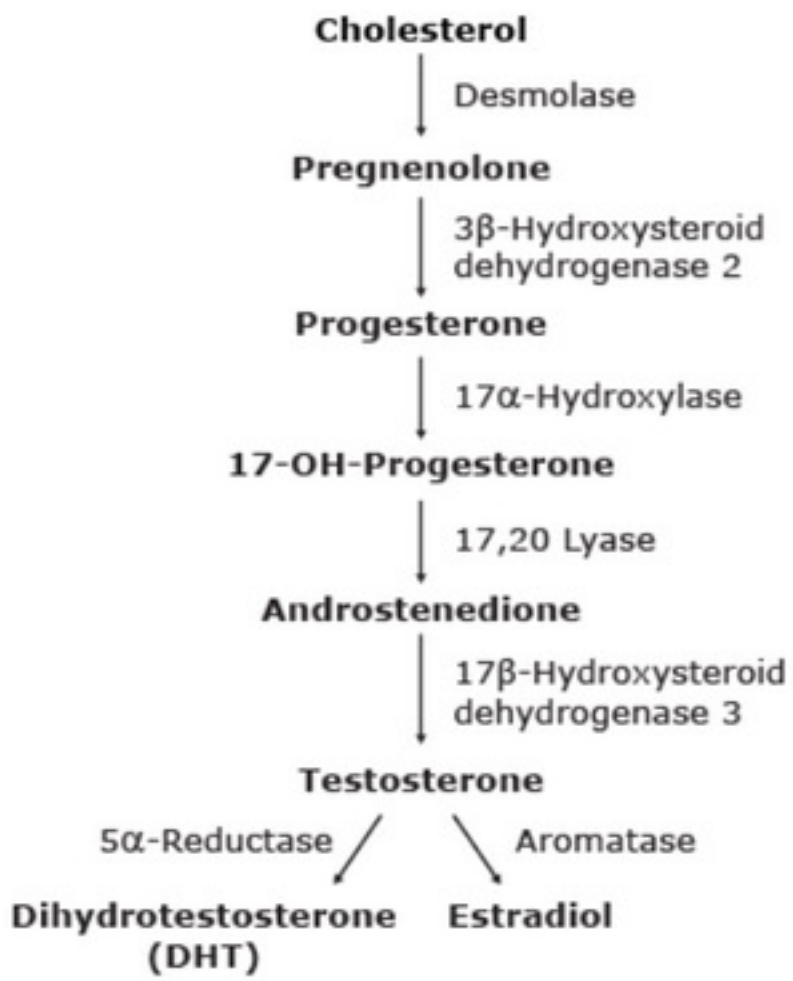
1.2 Leydig Cell Function

- Leydig cells are the primary endocrine cells of the testes. Their main function is the synthesis of testosterone.
- LH receptors are located on the Leydig cell's outer membrane. Anterior pituitary LH promotes Leydig cell growth and proliferation as well as stimulating the pathway from cholesterol to testosterone. A small amount of testosterone is converted into dihydrotestosterone (DHT).
- Testosterone and DHT are released into the circulation along with small amounts of the androgen precursors DHEA and androstenedione.
- Significant amounts of the testosterone diffuse into the Sertoli cells. Much of it becomes concentrated in the seminiferous tubules bound to an androgen-binding protein secreted by the Sertoli cells. The concentration within the tubules is about 100 times that of the plasma. This high concentration of testosterone is required for normal spermatogenesis. However, it is the Sertoli cells that have the receptors for testosterone, not the developing sperm cells.

Note: Injections of testosterone can never produce a high enough concentration within the seminiferous tubules to support spermatogenesis. Thus, functioning Leydig cells are required for a normal sperm count.



▲ **Figure 37–1.2** Testis Synthesis of Sex Steroids

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1.3 Sertoli Cell Function

- These are the epithelial cells of the seminiferous tubules. They extend from the basal lamina to the tubule lumen.
- They are the *nurse cells* for the developing sperm. The developing cells are guided from the basal region of the cell toward the luminal membrane where the motile sperm are released.
- Sertoli cells possess FSH receptors and FSH stimulates Sertoli function. Sertoli cells produce growth factors which facilitate sperm development and also synthesize and release the androgen-binding protein to the lumen of the seminiferous tubules.
- Sertoli cells also have aromatase activity and some of the Leydig cell testosterone is converted into estradiol. Sperm cells have estrogen receptors, and evidence indicates that the locally produced estrogen has some role that optimizes spermatogenesis. Some estrogen diffuses to the circulation. A Sertoli cell tumor greatly increases the circulating level of estrogen.
- Sertoli cells synthesize and release inhibin to the circulation. Inhibin creates the negative feedback loop that regulates the release of FSH.

In summary: For a normal sperm count, anterior pituitary LH is required to stimulate the Leydig cells in order to maintain the high local testosterone to support spermatogenesis. FSH is required to drive processes in the Sertoli for nurse cell mediation of sperm formation.

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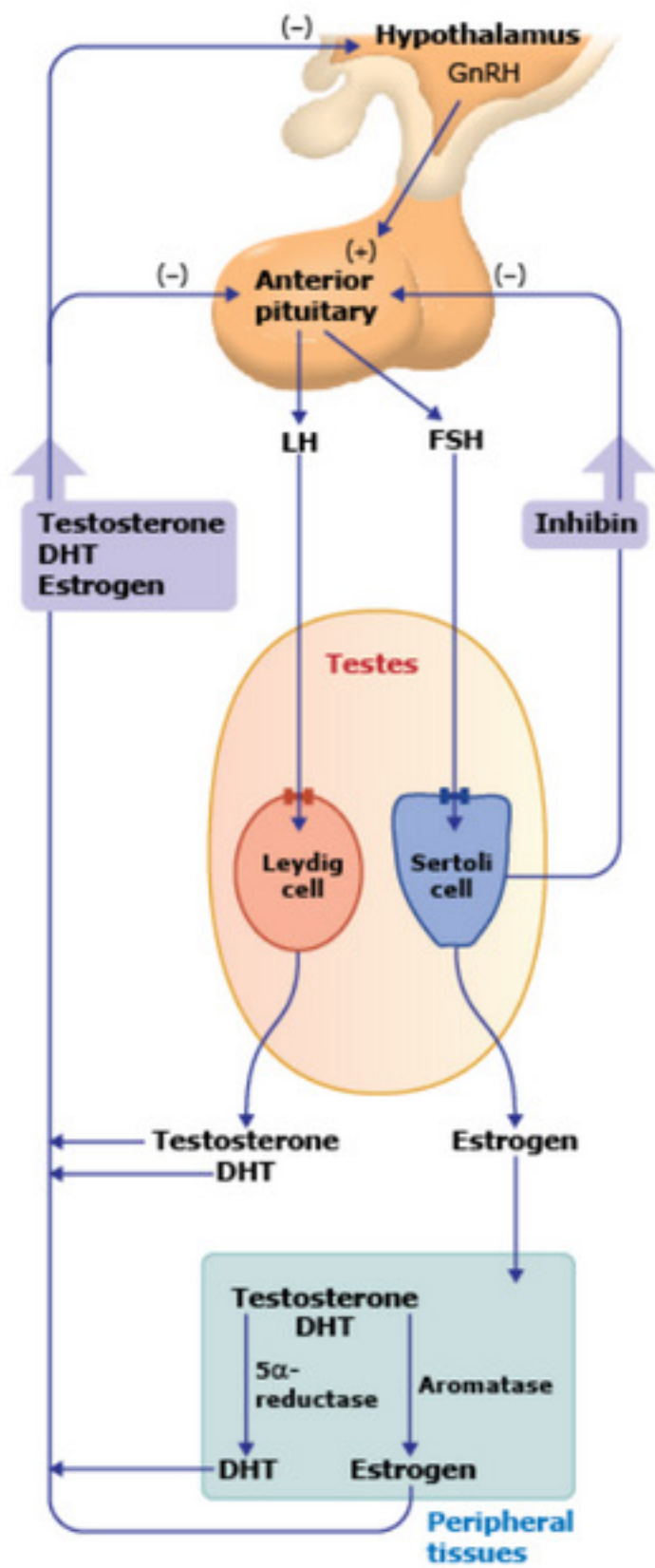
2 Hypothalamic—Pituitary—Testicular Axis

- Gonadotropin-releasing hormone (GnRH) is released in pulses from hypothalamic neurons, which terminate in the median eminence. When delivered to the anterior pituitary, there is a pulsatile release of LH and, to a lesser extent, FSH.
- The gonadotrophs of the anterior pituitary must receive a pulsatile input of GnRH. A constant delivery results in down-regulation of the GnRH receptors and a reduced LH and FSH secretion.
- LH and FSH are large glycoproteins (like TSH and hCG) which increases their circulating half-life (≈ 30 to 45 min.). They have an α and β subunit. The α subunits are the same with specificity based on β subunit structure.
- The target for LH is the Leydig cell, which it stimulates to secrete mainly testosterone but with some DHT. Testosterone and its metabolites, DHT and estradiol, feed back to inhibit the secretion of LH. They act at the level of the pituitary and the hypothalamus.
- The target cell for FSH is the Sertoli cell. FSH stimulates the synthesis and secretion of inhibin, which feeds back to the anterior pituitary to inhibit the release of FSH.

Note: Under physiological conditions, there are separate feedback loops for LH and FSH and independent control of the release of LH versus FSH. This is partly related to the pulsatile frequency of GnRH. High-frequency pulses favor LH; low-frequency pulses favor FSH.



▲ **Figure 37–2.0** Regulation of Male Hormone Secretion

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2.1 Actions of Testosterone

- In addition to its actions in the testes, testosterone has several metabolic actions in the periphery. It has a positive anabolic effect on muscle, promotes bone growth, and increases red blood cell production. It maintains erectile function and libido.
- There is peripheral conversion of testosterone to DHT by the enzyme 5α-reductase. There are two isoforms. 5α-reductase 1 expression occurs at puberty, and primarily in the skin. It contributes to sebaceous gland activity, which promotes acne. 5α-reductase 2 is expressed in the urogenital tract, hair follicles, and liver. It is the 5α-reductase 2 that generates the DHT required for the development of male external structures during fetal development and many of the changes associated with puberty. Most of the circulating DHT is the result of peripheral conversion from testosterone.
- Testosterone and DHT bind to the same androgen receptor, but DHT does so with a much higher affinity. DHT is therefore the more active form of the hormone.
- Testosterone circulates bound mainly to sex-steroid hormone-binding globulin (SHBG) 60%; most of the remainder is bound to albumin, and about 2% is free hormone diffusible to the tissues. SHBG is decreased by androgen, obesity, and nephrotic syndrome. Estrogen, hyperthyroidism, aging, and some chronic inflammation diseases elevate SHBG.
- When metabolized in peripheral tissues, testosterone is converted to a 17-ketosteroid, made water soluble and released back to the circulation. These metabolites are filtered and appear in the urine but most of the urinary 17-ketosteroids originate from adrenal androgens. Urinary 17-ketosteroids are not a good index of testicular testosterone synthesis.
- In addition to Sertoli cells, many peripheral tissues express aromatase, particularly adipose tissue. Like DHT, most of the circulating estrogen in men is the result of peripheral conversion from testosterone.

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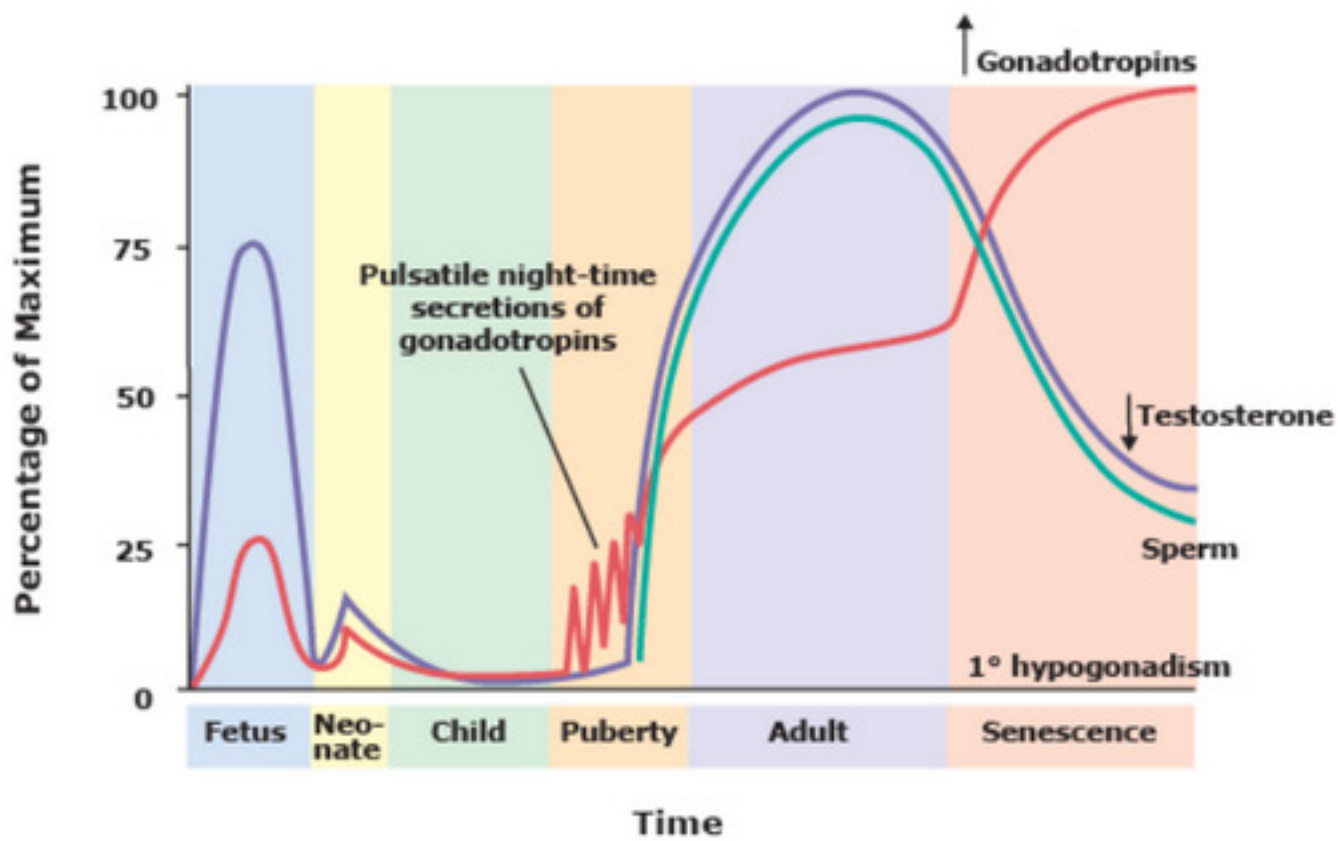
3 Sexual Differentation and Age-Related Changes in Testosterone Secretion

3.1 Fetus

- The embryonic gonad is bipotential and can develop into either a testis or an ovary depending on which genes are expressed. Several genes are involved in gonadal differentiation, development, and final positioning of the gonad. The ovarian development has been considered the *default* processes but specific genes are expressed and involve follicle development.
- Expression beyond gonadal development depends on hormonal input. Initially, the fetus is equipped with the primordial of both male and female ducts.
- Müllerian ducts potentially form the fallopian tubes, the corpus and cervix of the uterus, and the upper third of the vagina.
- Wolffian ducts potentially form the majority of male internal structures; the epididymis, vas deferens, seminal vesicles, and ejaculatory duct.
- Without hormonal input, the wolffian ducts regress and the müllerian ducts differentiate into female internal structures. Further, the absence of hormonal input results in female external structures.
- Normal male development requires the input of three hormones: Testosterone, DHT, and anti-müllerian hormone (AMH).



▲ **Figure 37–3.1** Male Hormone Secretion From Fetal Development to the Aging Adult

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- hCG, along with male fetus LH, stimulate the fetal testes Leydig cells to secrete testosterone. Fetal plasma testosterone reaches levels almost as high as in the adult male. Testosterone stimulates the wolffian ducts to develop into specific male internal structures.
- 5α-reductase 2 converts testosterone to DHT. DHT induces the urogenital sinus and genital tubercule to differentiate into the external scrotum, penis, and prostate gland. A 5α-reductase 2 deficiency results in ambiguous genitalia and in the extreme to female external structures.
- Anti-müllerian hormone secreted by the Sertoli cells prevents the development of the müllerian ducts into female internal structures. If the Sertoli cells fail to secrete AMH, in addition to other female internal structures, a small, non-endocrine-supported uterus will be present.
- In contrast to the testes, there is little evidence of hormone production by the fetal ovary.
- Summary of male development:
  1. Leydig cell → testosterone → wollfian ducts develop into male internal structures except prostate.
  2. Testosterone $\xrightarrow{5\alpha\text{-reductase 2}}$ dihydrotestosterone → male external structures and prostate.
  3. Sertoli cells → anti-müllerian hormone → müllerian ducts regress.

3.2 Neonate

- At term, gonadotropins are suppressed but estrogen clearance following delivery reduces inhibition, resulting in postnatal peaks in LH and FSH.
- Serum testosterone concentrations may be increased to as high as mid-puberal levels during the first several months following delivery in normal boys.

3.3 Child

- Period of quiescence of reproductive hormones. The mechanism is not known but it appears to involve a central nervous system restraint in GnRH secretion.

3.4 Puberty

- With puberty comes the gonadal sex steroids, the secondary sexual development, the growth spurt, and fertility.
- Hypothalamic pulse generator increases in activity in the peri-puberal period just before the physical changes begin.
- This drives an increase in gonadotropin secretion and the increase in LH stimulates the Leydig cells to again secrete testosterone.
- Leptin is a hormone produced by adipose tissue that suppresses appetite. Leptin is a necessary component of puberal development in humans. Individuals with a leptin receptor deficiency have disordered puberty.
- Obesity decreases the onset age of puberty, and chronic illness or malnutrition can delay puberty.

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3.5 Adult

- LH drives testosterone secretion and its metabolites, DHT and estradiol. All three feed back at the level of the hypothalamus and anterior pituitary to regulate LH secretion.

3.6 The Aging Adult Man

- There is no sharp *andropause* in men. Instead, there is a gradual decrease in total and free testosterone levels in the circulation.
- There are age-related changes in pituitary function. Studies have shown a decreased pituitary response to GnRH.
- The fact that declining testosterone levels are associated with increasing levels of LH (and FSH) suggests that Leydig cell dysfunction is the main cause of the declining androgen levels.
- Androgen supplementation is not currently recommended in older men because of possible adverse side effects.

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4 Overall Physical Changes at Puberty

4.1 Male Changes

- The first sign of puberty in boys is an increase in the size of the testes. Most of this increase is due to seminiferous tubular development by way of FSH stimulating Sertoli cells, with a small component of LH stimulating Leydig cells.
- Pubic hair results from adrenal and testicular androgen secretion.
- Boys develop more lean body mass, and greater skeletal and muscle mass.
- Boys establish reproductive maturity before physical and emotional maturity.
- The growth spurt occurs near the end of puberty.

4.2 Female Changes

- In girls, the growth spurt is at the beginning of puberty and the accelerated longitudinal growth is the first sign of puberty. This is not usually observed with an infrequent physical exam.
- The first noted sign of puberty is breast development. Breast development is stimulated mainly by the increasing estrogen but progesterone also plays a role.
- There also is enlargement of the labia minora and majora and dulling of the vaginal mucosa to a more pinkish color due to cornification. There is enlargement of the uterus.
- Girls develop more body fat.
- Pubic hair development is produced by adrenal and ovarian androgens.
- As with boys, reproductive maturity occurs before physical maturity.

4.3 Erection and Ejaculation

- Erection is a sacral parasympathetic response. This is the exception to the rule that parasympathetics do not affect the resistance of systemic arterioles.
- Acetylcholine, vasoactive intestinal peptide, and nitric oxide may be involved.
- As the sinuses become engorged with blood, the subtunical venous plexus is compressed against the tunica albuginea, preventing outflow of the blood.
- Emission is a sympathetic response which moves the semen from the epididymis to the vas deferens, the seminal vesicles, and the ejaculatory ducts.
- Stimulation of somatic neurons completes the process of ejaculation.

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5 Hypogonadism

- Androgen deficiency during development results in ambiguity of the genitalia.
- Androgen deficiency at puberty results in poor secondary sexual development and eunuchoidal skeletal proportions. The penis and testes do not enlarge. Voice stays high-pitched and there is a lack of muscle development and sparse axillary and pubic hair growth.
- Androgen deficiency after puberty may cause decreased libido, erectile dysfunction, and low energy. With long-standing hypogonadism, the growth of facial hair will diminish.

5.1 Laboratory Tests for Hypogonadism

- A normal semen analysis usually excludes gonadal dysfunction.
- The plasma level of SHBG should be taken into account when measuring testosterone. If SHBG is low, free testosterone should be measured.
- Gonadotropins are released in pulses, with a diurnal variation that is high in the morning. Several samples may be necessary and a single pooled sample analyzed.
- Hyperprolactinemia inhibits GnRH, promoting hypogonadism. This possibly should be considered in the evaluation.
- Primary hypogonadism: ↓ testosterone, ↑ LH ↑ FSH. Stimulation test is hCG. Failure of a rise in testosterone indicates a primary problem.
- If not primary, consider hyperprolactinemia or a secondary problem.
- Secondary hypogonadism: ↓ testosterone, ↓ or low normal LH. Stimulation test is GnRH. Failure of a rise in LH indicates a secondary problem or a tertiary problem with desensitized gonadotrophs.
- The solution to a tertiary problem would require a pulsatile delivery of GnRH to prevent down-regulation of the gonadotroph receptors.
- Methyl testosterone: ↑ plasma testosterone, ↓ LH, and if the plasma testosterone is a nonphysiological ↑, there can be a ↓ FSH. The ↓ LH causes atrophy of the Leydig cells, low testicular testosterone, and a low sperm count. Fertility can be regained with injections of hCG (or LH).

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5.2 Cryptorchidism

- This occurs with incomplete descent of the testes from the abdominal cavity.
- This impairs spermatogenesis. If bilateral, there is ↓ testosterone ↓ inhibins but ↑ LH and ↑ FSH.

5.3 Gynecomastia

- Refers to the enlargement of the male breast.
- All cases involve a relative imbalance between estrogen and androgen at the level of the mammary gland.
- Occurs normally in the male newborn due to placental transfer of estrogen. Occurs during puberty because of the high estrogen/androgen ratio in the early stages, and with aging as a result of the increased adipose tissue and increased aromatase.

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1 The Ovarian Follicle

- Premeiotic germ cells proliferate in the fetal ovary and are referred to as oogonia.
- Starting at about eight weeks of gestation, oogonia begin meiosis where they arrest in prophase I. They are now referred to as primary oocytes.
- The primordial follicles form and consist of a primary oocyte and a single layer of follicular cells (granulosa cells) and a basement membrane. They represent the fundamental reproductive units of the ovary that comprise a pool of resting oocytes. The granulosa cells establish gap junctions with each other and the oocyte. The gap junctions allow the transfer of various factors, nutrients, and waste products.
- Primordial follicles appear in mid-gestation, and initially about 7 million form. This decreases to about 300,000 to 400,000 at puberty. Approximately 450 will become dominate follicles and ovulate between puberty and menopause.
- Primordial follicles are lost due to atresia but a small pool enters follicular growth in waves. This is independent of pituitary gonatropins.
- Primordial follicle → Primary follicle: Growth of the oocyte and development of a zona pellucida, which is a thick layer of glycoprotein between the oocyte and granulosa cells → Secondary follicle: Proliferation of the granulosa cells now with FSH receptors and the acquisition of the outer thecal cells now with LH receptors. This is now a mature preantral follicle.
- Mature preantral follicles continue to grow and develop into early antral follicles (≈ 25 days). This growth is now FSH dependent. Granulosa cells increase to six to seven layers and a small fluid-filled antrum appears.
- As the antrum develops, it divides the granulosa cells into two populations. Mural granulosa cells line the outer antrum and remain in the ovary after ovulation to differentiate into luteal cells. In addition to FSH receptors, these cells in the follicular phase will develop LH receptors. Cumulus granulosa cells, which only have FSH receptors, are the inner cells that surround the oocyte and maintain oocyte contact through gap junctions. Cumulus granulosa cells are released with the oocyte at ovulation and play a role in the capture by fimbriae.

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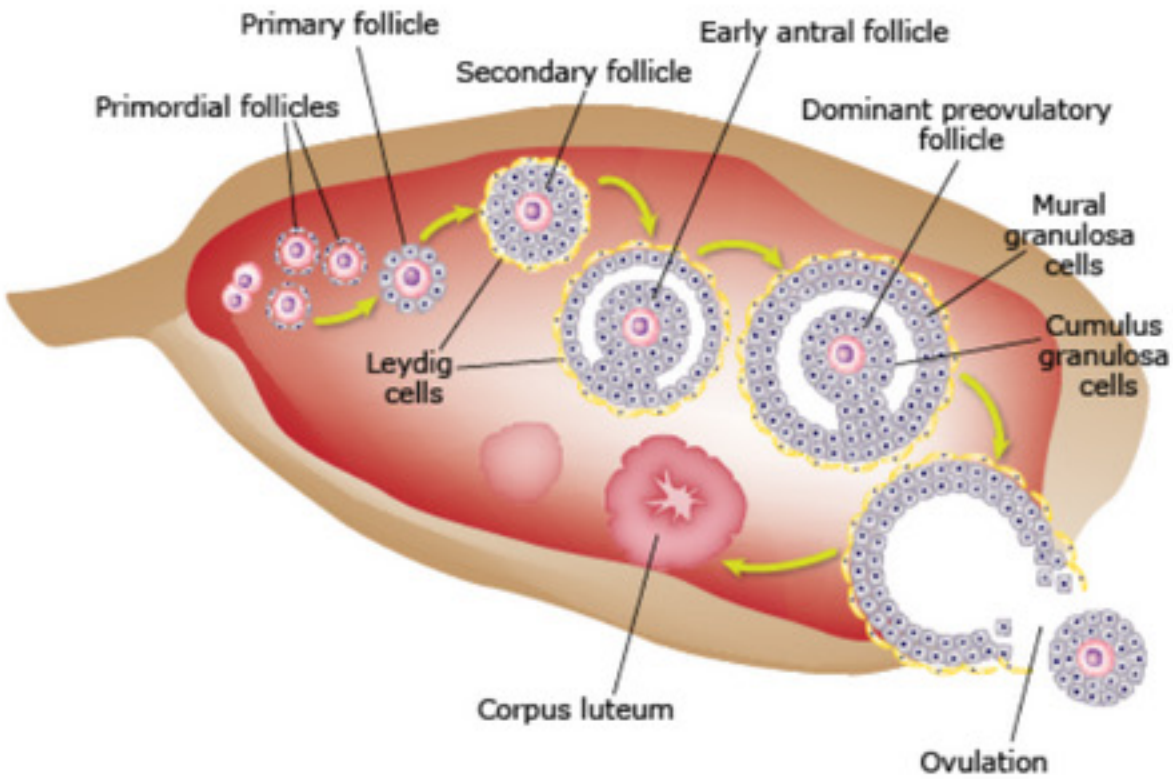
- Large antral follicles are dependent on FSH for growth and viability. In the mid-luteal phase of the menstrual cycle, a group of large antral follicles are recruited to begin a rapid FSH-driven development. This can be as high as 20 in a younger woman. By a process of selection, one becomes the *dominant steroidogenic follicle* in the first week of the follicular phase. Generally, it is the largest follicle with the greatest number of FSH receptors. This follicle enlarges greatly in the latter follicular cycle just before ovulation. In some women, this causes some discomfort in the pelvic region.
- The dominant preovulatory follicle completes meiosis I a few hours before ovulation, extrudes the first polar body and arrests in metaphase II (secondary oocyte). Meiosis is completed with fertilization and the second polar body is extruded, producing a haploid ovum.



▲ **Figure 38–1.0** Stages in the Development of the Ovarian Follicle

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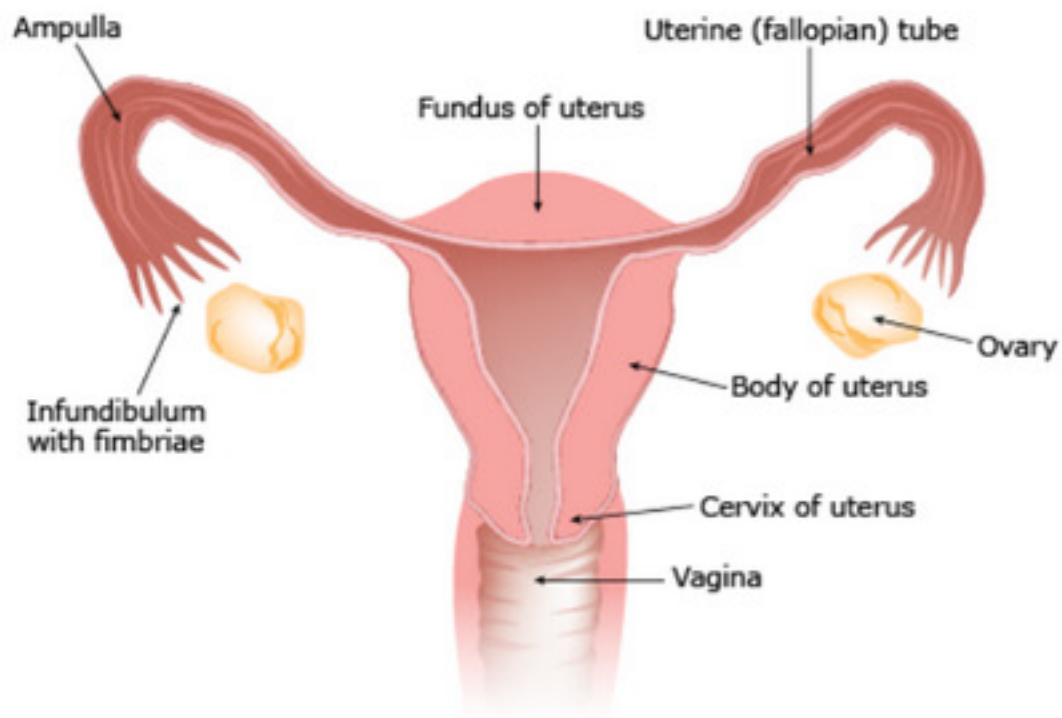
2 The Female Reproductive System and Uterine Cycle



▲ **Figure 38–2.0A** Ovarian-Uterine System

- Oviducts (uterine tubes, fallopian tubes): Muscular tubes with openings close to the ovaries. The finger-like projections are the fimbriae, which sweep the surface of the ovary. They capture the cumulus-oocyte which then moves to the ampulla, where fertilization usually takes place.
- Oviducts can store sperm and initiate fertilization for five days.
- Following fertilization and the initial development of the blastocyst, the oviducts slowly move it toward the uterus via a mucociliary tract. The blastocyst needs to reach the uterus about five days after fertilization. In the first week of the luteal phase, progesterone along with some estrogen prepares a secretory endometrium. At that point (mid-luteal phase) the uterus is ready for implantation. The function of the uterus is to support a developing fetus.
- The uterus has two main layers: An inner muscular myometrium and, toward the lumen of the uterus, an endometrium. It is the endometrium that differentiates during the menstrual cycle.
- The endometrium has two layers. The deeper *basalis layer* is the origin of the more superficial *functionalis layer,* which develops with each menstrual cycle. The functional layer is lost in menstruation.
- Estrogen secreted in the follicular phase (= proliferative phase) initiates the formation of a new functional layer. This layer develops estrogen and progesterone receptors. Spiral blood vessels from the basal layer extend through and supply nourishment to the functional layer.

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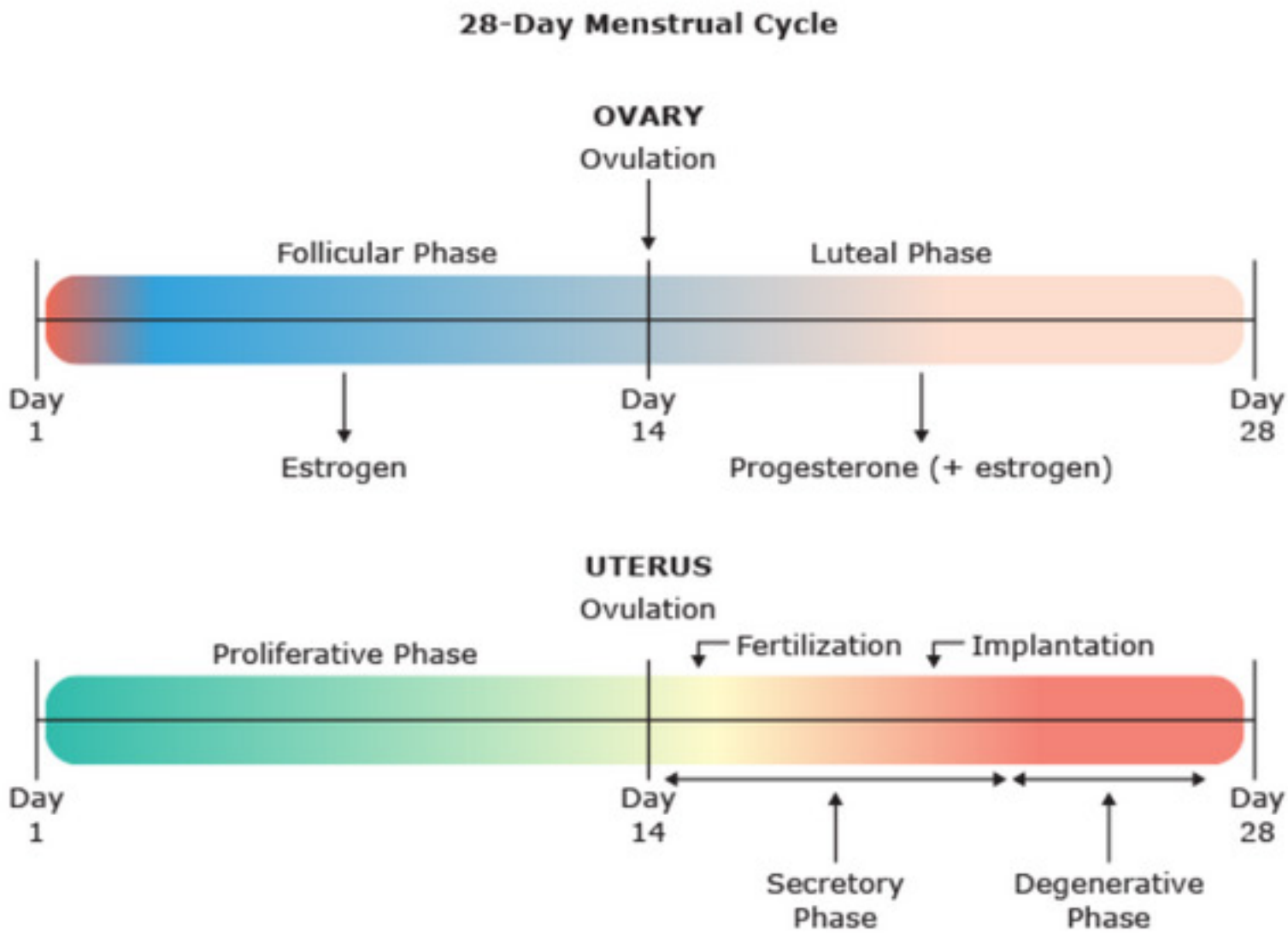
- In the luteal phase, progesterone inhibits further endometrial proliferation and generates a secretory endometrium. This fluid provides the initial nourishment to the implanted blastocyst.
- Implantation has only a three-day window in which the endometrium is sufficiently thick and filled with supporting fluid for the blastocyst.
- If no implantation occurs there is a degenerative phase, due to withdrawal of the support of progesterone. This initiates prostaglandin production. Prostaglandins cause cyclical vasoconstriction and relaxation of the spiral arteries in the functional layer. This leads to ischemia-reperfusion injury and finally hemorrhage. The functional layer becomes necrotic and sloughs away as menstruum.



▲ **Figure 38–2.0B** Correlation of the Ovarian and Uterine Phases of the Menstrual Cycle

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3 The Ovarian Menstrual Cycle

- The ovarian menstrual cycle is approximately 28 days. It consists of two phases and one event. Each of the two phases is about 14 days. Day 1, by definition, is the first day of menses. Variable lengths in the menstrual cycle are usually due to variations in the follicular phase. Once ovulation occurs, menstruation occurs almost exactly 14 days later. The length of the menstrual cycle in days minus 14 gives a good estimate of the day of ovulation.
- **Follicular Phase:** Days 1–14—This represents the growth of the dominant follicle within the ovary, driven mainly by FSH. The main hormonal secretion is estrogen by the granulosa cells. One function of the estrogen is to stimulate the replacement of the cells of the functional layer of the endometrium lost in the last menstruation.
- **Ovulation:** Preceded by the LH surge near the end of the follicular phase, which induces ovulation on about Day 14.
- **Luteal Phase:** Days 14–28—Formation and functioning of the corpus luteum, driven by LH. The main function of the corpus luteum is to secrete progesterone plus some estrogen. The estrogen is needed for progesterone to function. The progesterone secreted in the first week of this phase creates the thick, secretory endometrium required for implantation. If implantation does not occur there is, in the final days of this phase, necrosis and sloughing of the functional endometrium.

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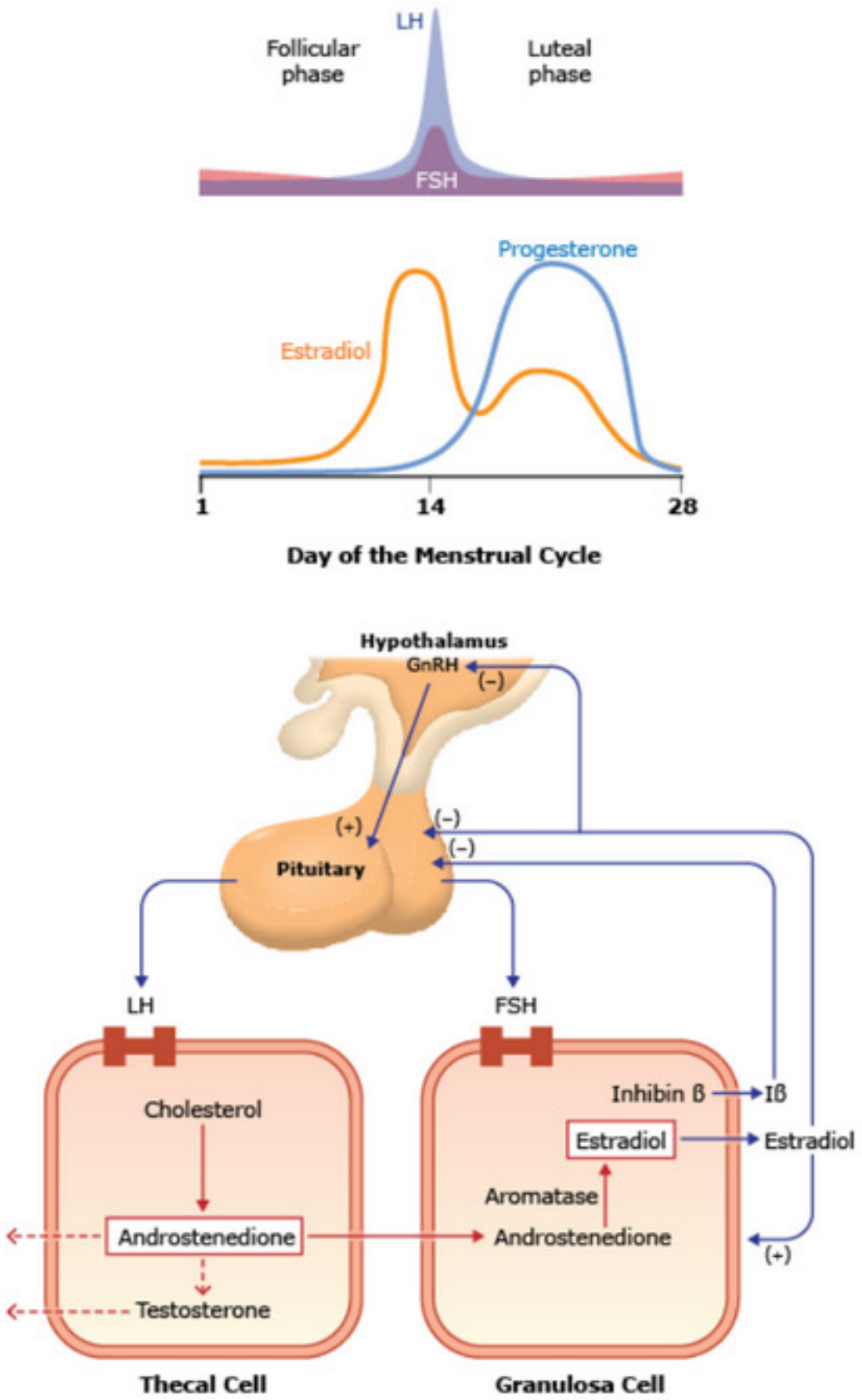
3.1 Follicular Phase



▲ **Figure 38–3.1** Hormone Secretions of the Follicular Phase

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A dominant follicle emerges from the growing pool of follicles in the first week of the follicular phase. As stated earlier, this is probably the largest follicle and the one with the greatest number of FSH receptors. The dominant follicle undergoes rapid enlargement during the last week of the follicular phase prior to ovulation. There is granulosa cell proliferation and accumulation of antral fluid. The dominant follicle becomes a steroidogenic gland. Both the thecal and granulosa cells are required and participate in steroid hormone synthesis (two-cell model).

Thecal Cells: Have LH receptors and stimulation by LH; they produce large amounts of androgen. The main androgen synthetized is androstenedione, but some testosterone is also synthetized. Some androgen diffuses to the circulation but most is transferred to the granulosa cells.

Granulosa Cells: Mural granulosa cells are very sensitive to FSH. They express aromatase and convert the androgen to estrogen. Enzymes drive the overall pathway toward 17β-estradiol, which then enters the circulation. Some estrone is also produced. The rise in estrogen within the follicle further augments FSH activity. In other words, estrogen acting locally enhances its own production. FSH also stimulates the production and secretion of inhibin β. Inhibin acting on the pituitary inhibits the secretion of FSH. Circulating estrogen acting on the pituitary and the hypothalamus inhibit the secretion of both LH and FSH. But because of the local effect of estrogen in the ovary, it continues to rise throughout this phase. Estrogen slowly rises at the beginning and then increases more rapidly near the end of the phase. FSH also induces the development of LH receptors on the mural granulosa cells in the latter half of the follicular phase.

Estrogen: Estrogen has some important peripheral actions during this phase. As mentioned earlier, it induces the replacement of the cells of the functional endometrium lost in the last menstruation. It also causes the cervical mucus to be thin and watery. This facilitates the transport of sperm.

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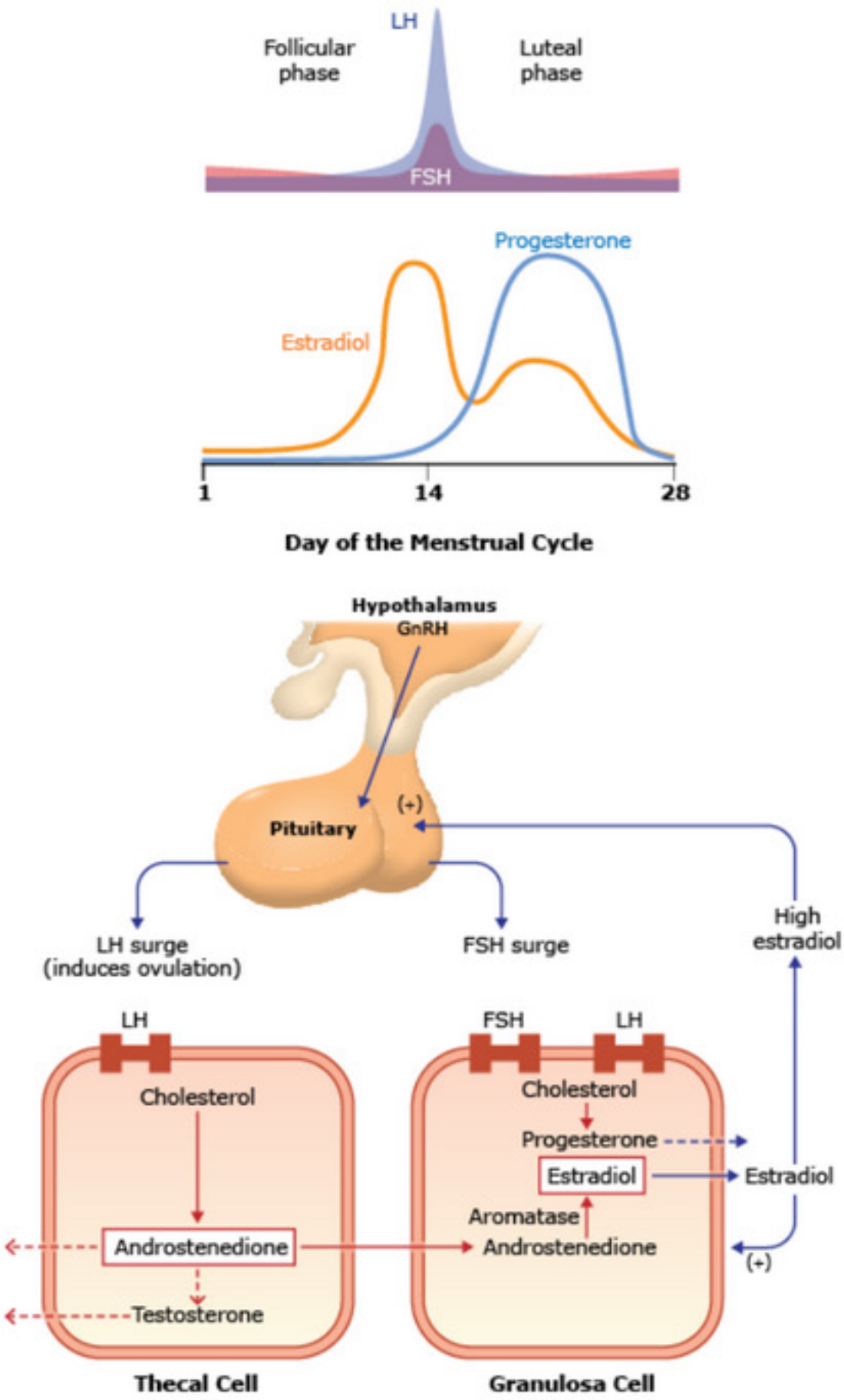
3.2 Ovulation



▲ **Figure 38–3.2** Hormone Secretions and Ovulation

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Preovulatory Follicle: The large graafian follicle moves toward the outer surface of the ovary and presses against the surface in preparation for ovulation. The attachment of the cumulus granulosa cells to the mural granulosa cells is broken. The cumulus-oocyte complex is now free-floating within the antral cavity. The LH surge causes enzymatic breakdown of the follicular wall and the ovary surface, resulting in the antral cavity becoming continuous with the peritoneal cavity. This permits the release of the cumulus-oocyte complex. Before release there is enlargement of the cumulus-oocyte and completion of meiosis I. It arrests in metaphase II. In addition, the steroidogenic pathways start to change just before ovulation. They begin to move away from producing estrogen and toward a greater production of progesterone. As a result, plasma progesterone begins to rise just before ovulation. Progesterone also increases basal body temperature and it has been used as a marker of ovulation. As mentioned previously, the mural granulosa cells develop LH receptors in the latter week of the follicular phase.

Ovulation: Estrogen, initially in the follicular phase, creates a negative feedback loop and inhibits the release of LH and FSH. However, with the late dramatic rise in estrogen, it no longer inhibits the release of LH and FSH—it stimulates their release. In other words, a negative feedback has been converted to a positive feedback. This results in an LH and an FSH surge but it is the *LH surge* that causes ovulation. The FSH surge may be involved in recruiting a new cohort of follicles for the next cycle.

Note: Estrogen peaks just before the LH surge. Thus, if estrogen is high but still rising, the LH surge has not occurred, and ovulation has not occurred. Ovulation takes place about 36 hours after the LH surge. Because LH is a protein hormone, it is filtered by the kidney and appears in the urine. The appearance of an increase in urine LH can be used as an indicator of impending ovulation.

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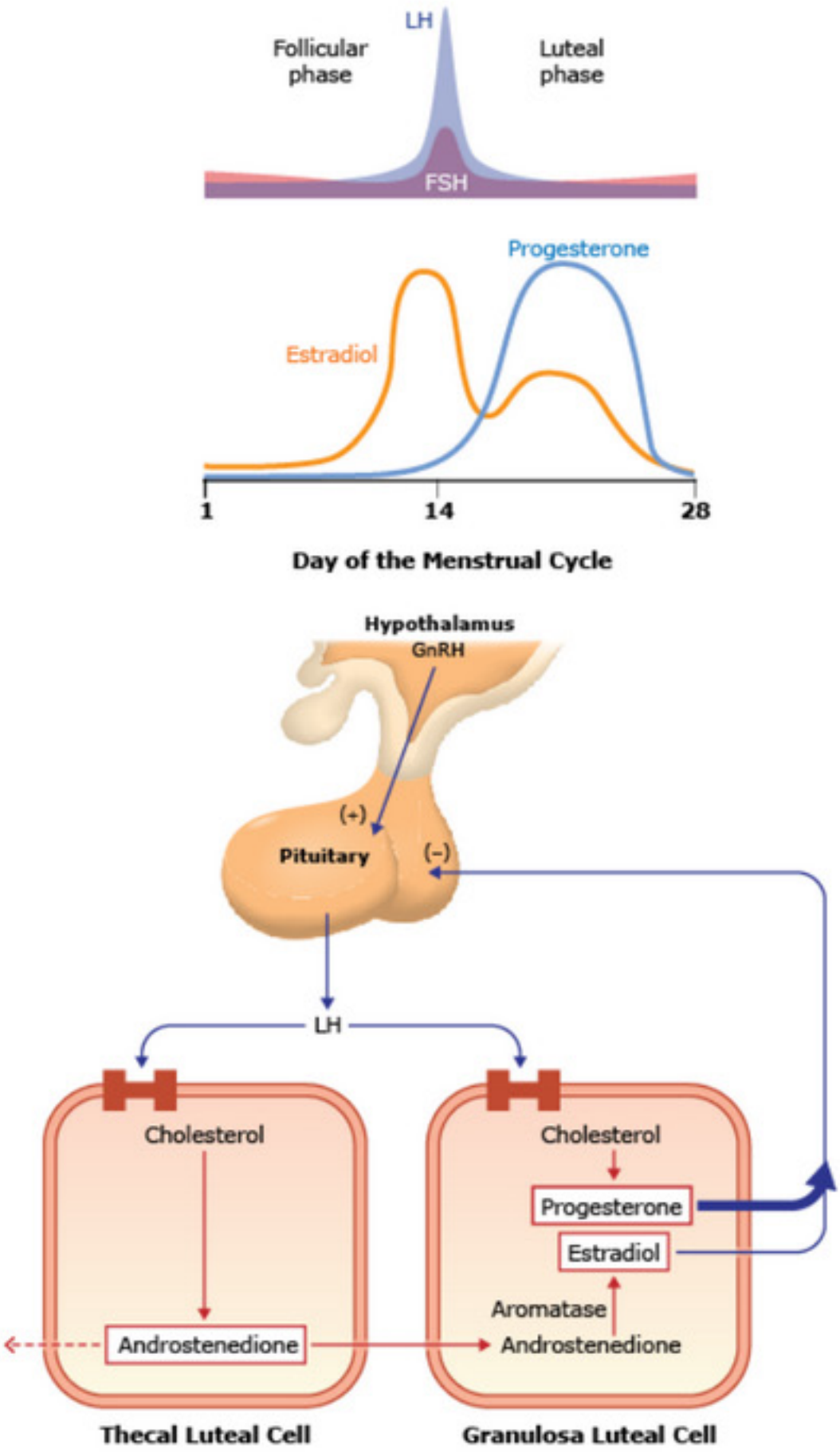
3.3 Luteal Phase



▲ **Figure 38–3.3** Hormone Secretions of the Luteal Phase

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Luteal Phase: In response to the LH surge, the remaining cells of the follicle transform into luteal cells. The luteal cells upregulate their LH receptors. This allows the basal secretion of LH to stimulate and maintain the corpus luteum.

The luteal cells pathways produce considerable progesterone and some estrogen. Inhibin A also is secreted by the corpus luteum. The secreted progesterone inhibits the secretion of LH.

Progesterone rises and peaks about the midpoint in the luteal phase. During the first week of the luteal phase, the progesterone along with estrogen creates the secretory endometrium. This prepares the uterus for implantation.

Progesterone also causes the cervical mucus to become thicker. This makes it more difficult for sperm as well as bacteria to penetrate the uterus.

3.4 Menses

The corpus luteum starts to undergo a programmed cell death (luteolysis) approximately nine days after ovulation. The origin of luteolysis is not understood. For some reason, the luteal cells stop responding to LH. The resulting decrease in progesterone withdraws support for the functional endometrium. Thus, menstruation can be considered a passive process.

3.5 Monitoring the Menstrual Cycle

- As mentioned previously, an increase in urine LH is an indication of the approaching ovulation.
- Estrogen and progesterone are lipid-soluble hormones and, as such, limited amounts appear in the urine. However, during their metabolism (e.g., in liver) they are conjugated with a glucuronide or sulfate group and become water soluble. These water-soluble metabolites can be followed in the urine.
- Low progesterone metabolites and low but slowly rising estrogen metabolites represent the early follicular phase.
- Low progesterone metabolites but rapidly rising estrogen metabolites represent the latter follicular phase just before ovulation. If estrogen is still rising, the LH surge has not yet begun. If estrogen has just peaked, the LH surge should start almost immediately and, about 36 hours later, expect ovulation.
- Elevated and rising progesterone metabolites are indicative of the first week of the luteal phase before implantation (this could also be pregnancy).
- Elevated but declining progesterone metabolites indicate the last week of the luteal phase.

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3.6 Estrogens

There are three natural estrogens:

1. **17β-estradiol:** This is the most potent estrogen and the main estrogen secreted by the ovary.
2. **Estrone:** It is formed in the ovary and some is released during the menstrual cycle, but it also is formed in peripheral tissues from androgens. It is the main circulating estrogen following menopause (1/10 the potency of estradiol).
3. **Estriol:** This is the main estrogen secreted by the placenta during pregnancy from circulating adrenal androgens. It is the least potent of the estrogens (1/100 the potency of estradiol).

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4 Pregnancy

4.1 Fertilization and Implantation

- Fertilization takes place within two days after ovulation in the fallopian tubes. Low sperm counts reduce fertility. With low counts, many sperm often have low motility and an abnormal morphology. A sperm count is one of the first tests to perform in the case of infertility.
- The embryo begins development as it is transported to the uterus, and by implantation it has reached the blastocyst stage (about five days after fertilization).
- At the time of implantation, the uterus is at its full thickness for the menstrual cycle and progesterone is high (mid-luteal phase). A high level of progesterone is absolutely required to maintain pregnancy. It provides a quiescent myometrium (noncontractile) and maintains the secretory function.
- Following implantation, the outer trophoblasts of the embryo differentiate, and the outer-most layer becomes the multinuclear/multicellular syncytiotrophoblasts that have a major endocrine function.
- Weeks of gestational age are, by convention, calculated from the first day of the last menstrual period. Biological pregnancy begins two weeks later with fertilization. Thus, fetal age is always two weeks less than gestational age.

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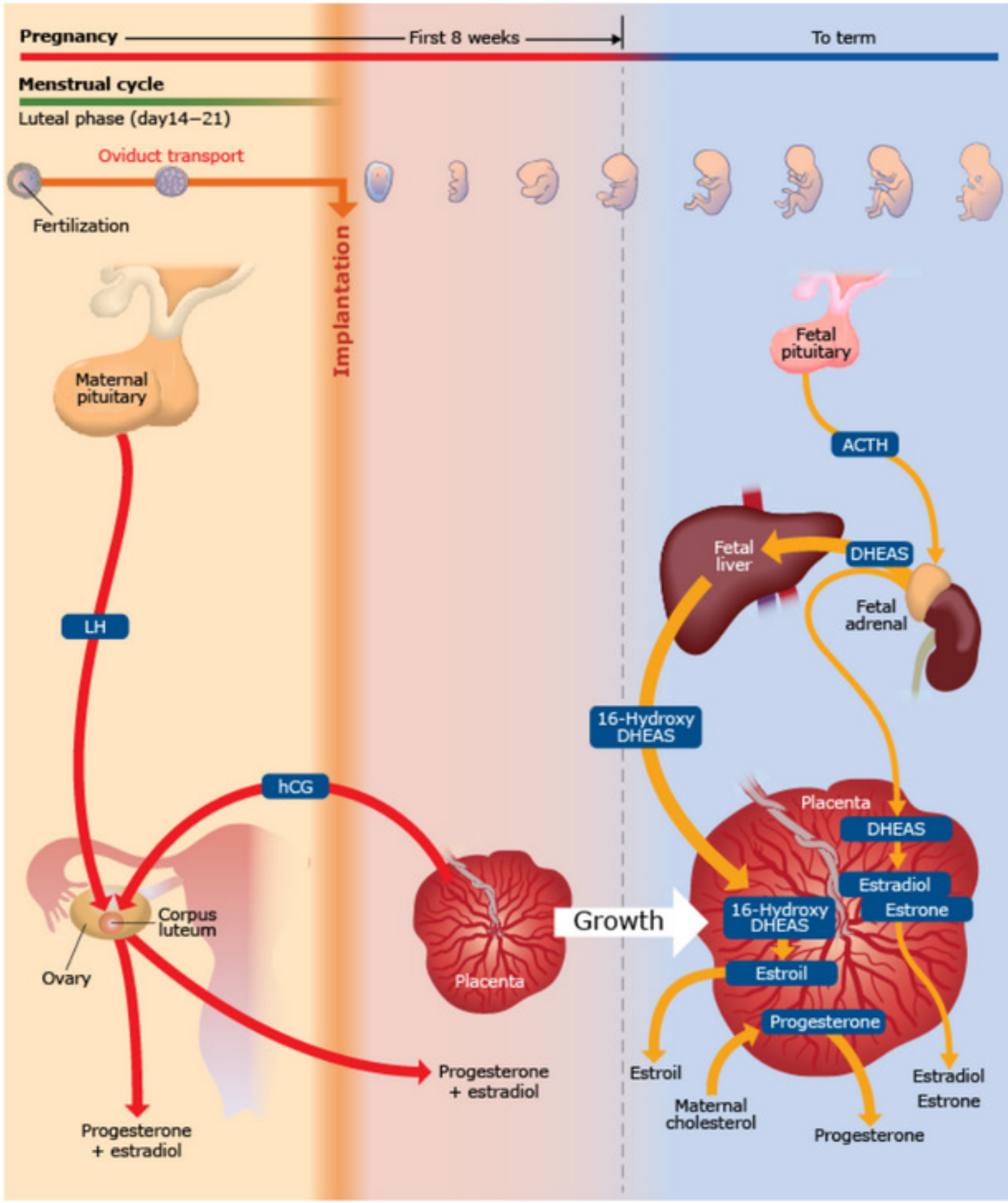
4.2 Hormonal Maintenance of Pregnancy



▲ **Figure 38–4.2** The Hormonal Maintenance of Pregnancy

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4.2.1 Early Pregnancy—First Two Months

- Week 1 of the luteal phase prepares the uterus for implantation. Pituitary LH → luteal cells → mainly progesterone and some estrogen (estradiol).
- At implantation, the luteal cells are losing sensitivity to LH. Almost immediately, the syncytiotrophoblasts begin synthesizing and secreting into the maternal circulation human chorionic gonadotropin (hCG).
- hCG is almost identical to LH. It has the same α-subunit and an almost identical β-subunit, and it will stimulate LH receptors.
- The important point is that the luteal cells program changes that lead to luteolysis, including an initial loss of sensitivity to LH, but the receptors maintain a sensitivity to hCG. The hCG *rescues the corpus luteum*. It prevents luteolysis and maintains the progesterone and estrogen secretion in early pregnancy.
- hCG is absolutely required to maintain the first eight weeks of pregnancy. Removal of the ovary containing the corpus luteum in the first seven to eight weeks of pregnancy aborts the developing fetus.
- hCG can be detected in the maternal circulation one day after implantation and within one week in the urine using a home-test kit for pregnancy. Its concentration peaks in the first three months of pregnancy, but a reduced secretion continues through the remainder of pregnancy.
- hCG has a weak affinity for the TSH receptor but there is no significant hyperthyroidism; only bound thyroid hormone is elevated due the effect of estrogen on the binding globulin. Excessively high hCG can induce a state of thyrotoxicosis.
- Because the placenta does not, but the corpus luteum does, secrete 17-hydroxyprogesterone and also relaxin, they can be used as indices of corpus luteal function. Both drop after the first trimester. hGC *cannot* maintain pregnancy into the second trimester.

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4.2.2 Late Pregnancy—Third Month to Term

- The placenta takes over the production of progesterone and estrogen.
- Progesterone production is independent of fetal tissues. Maternal cholesterol is the substrate and it is converted to progesterone with no feedback control. Maternal progesterone rises continuously throughout the remainder of pregnancy. Because fetal tissues are not involved in the synthesis of progesterone, this cannot be used as an index of fetal health.
- Estrogens are synthesized by the fetal syncytiotrophoblasts. They are similar to granulosa cells in that the precursors are androgens. The androgen synthesizing cells reside in the inner region of the fetal adrenal cortex. They represent about 80% of the large fetal adrenal. The major end-product is DHEA-sulfate, and its production is dependent on fetal ACTH. Interestingly, the placenta secretes CRH (cortictropin-releasing hormone) into the fetal circulation, which drives ACTH secretion. ACTH not only drives cortisol secretion but also fetal-placental estrogen secretion.
- DHEAS has two fates. When delivered directly to the placenta, it is converted into estradiol and estrone. In the liver, it is converted into 16-hydroxy-DHEAS, then delivered to the placenta, where it is converted to the main estrogen, estriol. Because estrogen synthesis is dependent on fetal tissues, it can be used as an index of fetal health and placental function.
- Rising serum or urinary estroil were once used as an index of fetal health.
- Maternal administration of glucocorticoids inhibits fetal ACTH and lowers maternal estriol.

4.3 Effects of Estrogens and Progesterone

- Estrogens increase the circulating steroid-binding globulins, elevating the bound steroid hormone in the circulation.
- Estrogen induces a hyperplasia of the lactotrophs and drives an increase in prolactin secretion, but estrogen blocks the action of prolactin. There is no significant milk synthesis during pregnancy. The anterior pituitary enlarges but there is no accompanying increase in vascularization of the pituitary, which makes it more vulnerable to ischemia with hypotension. As estrogens rise, prolactin rises. Both peak in the maternal circulation at term.
- Both estrogen and progesterone stimulate the growth of the uterus and all components of the breast during pregnancy.

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4.4 Human Placental Lactogen (hPL, Human Chorionic Somatomammotropin)

- Produced by the syncytiotrophoblasts and secreted mainly in the latter part of pregnancy. Not detected in the plasma until the 2nd month of pregnancy. The quantity of hormone secreted is directly related to the size of the placenta. Thus, the plasma levels rise throughout pregnancy.
- Has a structure similar to growth hormone and prolactin. It has the stress effects of growth hormone, mobilizes glucose and fatty acids in the maternal circulation, but has few growth-promoting actions.
- The fetus has the greatest growth and demand for substrates in the latter part of pregnancy. The main apparent role of this hormone is to supply those needs.
- Like growth hormone, hPL increases lipolysis and decreases the peripheral uptake of glucose. The developing fetus has a high demand for glucose, and a shift in maternal metabolism toward fatty acids spares the glucose for fetal development.
- The anti-insulin effect of hPL contributes to the insulin resistance and hyperinsulinemia of pregnancy, which can lead to the appearance of type 2 diabetes. If the diabetes resolves upon delivery, it is referred to as gestational diabetes.
- With a diabetic mother, the hyperglycemia often causes a high birth weight. The greater transfer of glucose to the fetus produces a greater insulin secretion (↑ of an anabolic hormone).
- HPL concentrations were used historically as an index of placental function. Normal values have a wide variation and hPL no longer is used as a clinical index.

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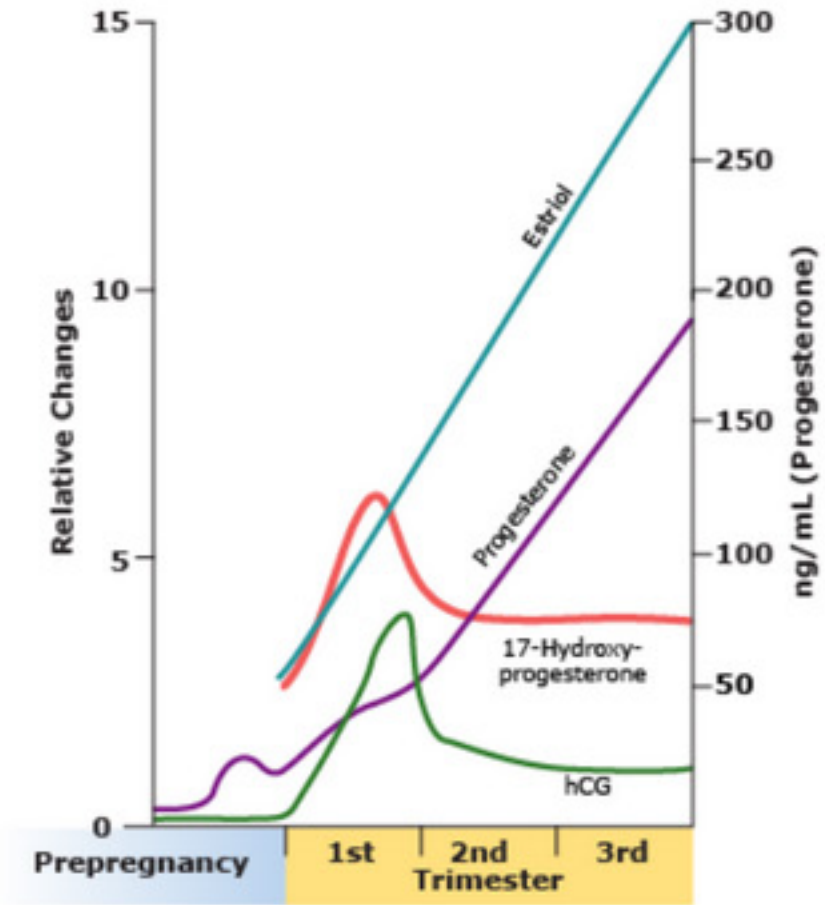
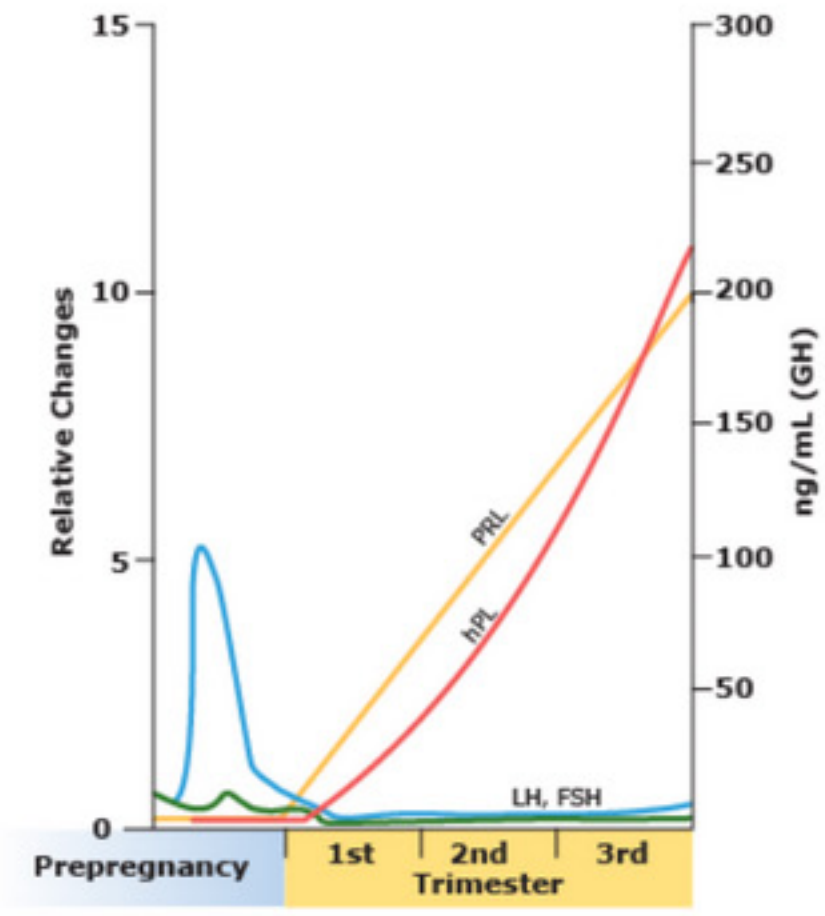
4.5 Overall Hormonal Changes During Pregnancy





▲ **Figure 38–4.5** Plasma Hormone Levels During Pregnancy

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- There is a progressive rise in progesterone and estriol during pregnancy. Estradiol and estrone show similar increases but at lower concentrations.
- hCG peaks in the first trimester but continues to be secreted throughout pregnancy. The pattern is similar for 17-hydroxyprogesterone, an index of the functioning of the corpus luteum.
- Pituitary gonadotropins are suppressed during pregnancy.
- Prolactin rises parallel to estrogen.
- hPL begins to rise in early pregnancy but the greatest plasma levels are in the latter part of pregnancy.

4.6 Adaptations to Pregnancy

- The placental circulation represents a large parallel circuit added to the systemic system. This causes a significant decrease in TPR. There is a compensatory increase in cardiac output (circulating volume) and venous volume. RBC production increases, but there is a slight decrease in HCT.
- Blood pressure is slightly decreased up to the third trimester, then there is a return to pre-pregnancy levels.
- Heart rate slowly increases throughout pregnancy.
- GFR is elevated and renal threshold decreases.
- Alveolar ventilation increases, mainly due to an increase in tidal volume.

4.7 Parturition

- When labor nears there are sporadic contractions of the uterus, and the lower uterus and cervix become softer, thinner, and more distensible.
- The onset of labor is usually sudden, with regular contractions every two to five minutes. The initiating event is unknown. One of progesterone's functions is the maintenance of a relaxed uterus, and a functional withdrawal of the effects of progesterone has been proposed as a mechanism inducing labor. There is no decrease in maternal plasma progesterone levels before labor.
- Prior to labor, oxytocin receptors appear in the myometrium, mainly due to estrogen. Once the receptors are present, oxytocin can be administered to induce labor but a rise in oxytocin does not occur until the fetus is already in the birth canal. Following delivery, oxytocin does cause the uterus to contract, minimizing blood loss.
- There is no evidence that prostaglandins initiate labor but they play a role in its maintenance. Prostaglandin E3 administered vaginally in the third trimester can induce labor.

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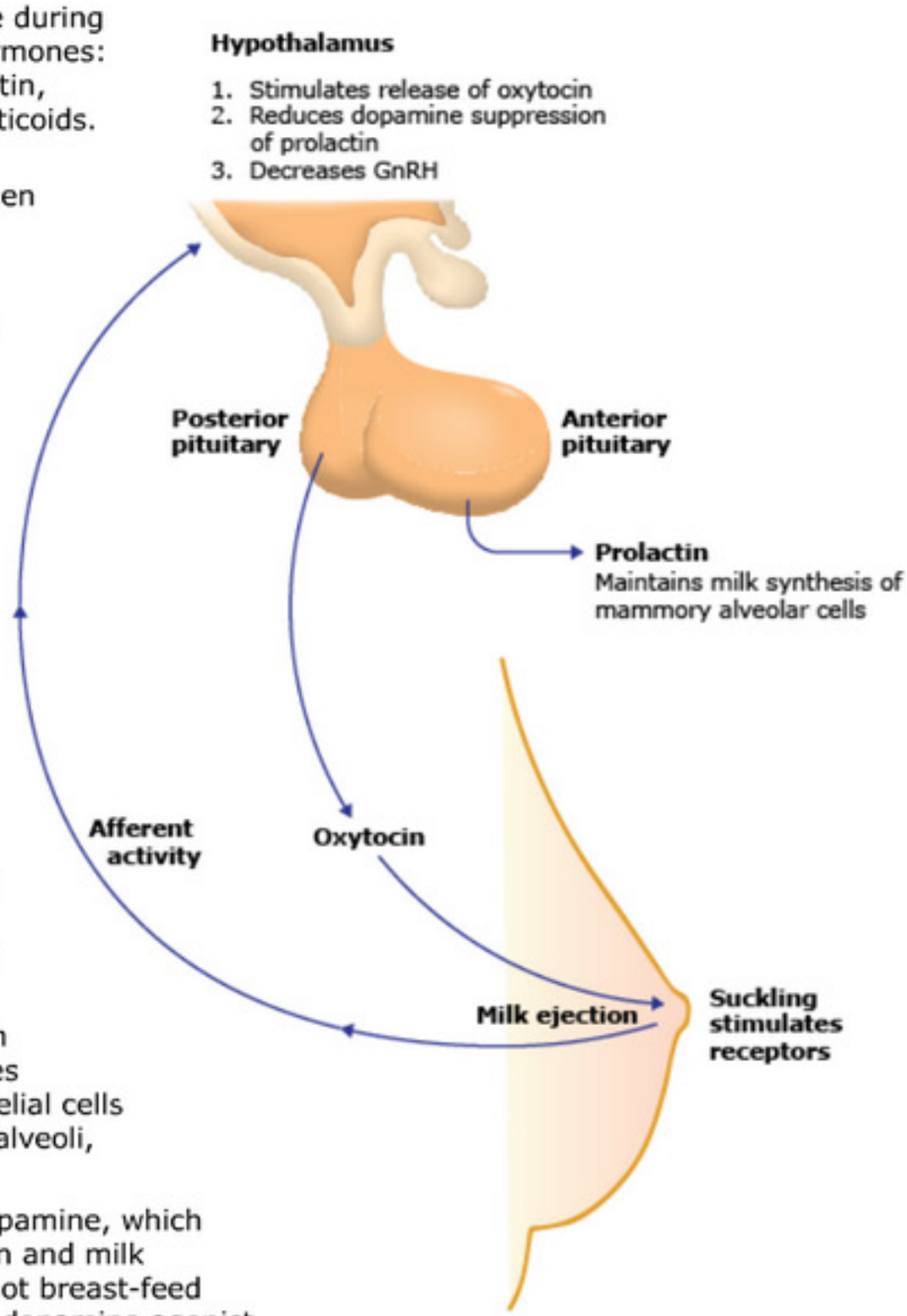
4.8 Lactation

- Growth of the mammary tissue during pregnancy involves several hormones: Estrogen, progesterone, prolactin, growth hormone, and glucocorticoids. HPL also may play a role.
- During pregnancy, the ↑ estrogen drives a ↑ prolactin. Both hormones peak at term. However, estrogen blocks the action of prolactin and there is no significant milk synthesis during pregnancy.
- At delivery, the decrease in estrogen removes the block and milk synthesis is initiated, but suckling by the newborn is required to maintain lactation.
- Milk ejection is known to occur by psychological stimuli, such as a mother hearing a baby cry, but it is normally a neuro-hormonal reflex. Tactile or mechanoreceptors in the nipple region increase afferent activity to the hypothalamus. The afferent activity has three main effects:

1. The release of oxytocin from the posterior pituitary causes contraction of the myoepithelial cells surrounding the mammary alveoli, producing milk ejection.
2. Decreases the release of dopamine, which maintains prolactin secretion and milk synthesis. Women who do not breast-feed their infants can be given a dopamine agonist (e.g., bromocriptine). However, adverse side effects make this application unadvisable.
3. Decreases the release of GnRH, causing in some cases a functional amenorrhea, which has been termed *nature's contraceptive*. Prolactin itself will decrease the release of GnRH.



▲ **Figure 38–4.8** Neuro-Hormonal Reflex of Lactation.

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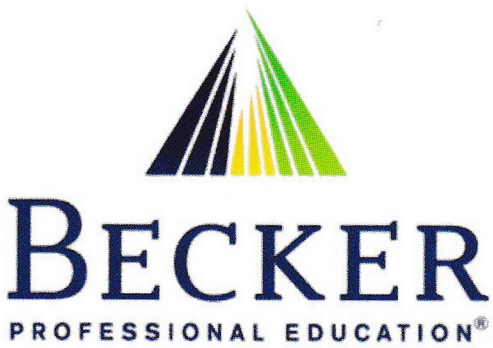
USMLE STEP 1 REVIEW



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